Validation and Qualification in Analytical Laboratories

Second Edition

Ludwig Huber

informa
healthcare

Validation and Qualification in Analytical Laboratories

Validation and Qualification in Analytical Laboratories

Second Edition

Ludwig Huber
Agilent Technologies
Waldbronn, Germany

informa
healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

Printed in the United States of America on acid-free paper
10 9 8 7 6 5 4 3 2 1

International Standard Book Number-10: 0-8493-8267-X (hardcover : alk. paper)
International Standard Book Number-13: 978-0-8493-8267-3 (hardcover : alk. paper)

Visit the Informa Web site at
www.informa.com

and the Informa Healthcare Web site at
www.informahealthcare.com

Library of Congress Cataloging-in-Publication Data

Huber, Ludwig, 1948-
Validation and qualification in analytical laboratories / Ludwig Huber. – 2nd ed.
p. ; cm.
Includes bibliographical references and index.
ISBN-13: 978-0-8493-8267-3 (hardcover : alk. paper)
ISBN-10: 0-8493-8267-X (hardcover : alk. paper) 1. Chemistry, Analytic–Quality control. 2. Chemical laboratories–Standards. I. Title.
[DNLM: 1. Chemistry, Pharmaceutical–standards. 2. Chemistry, Analytical–standards. 3. Drug Industry–standards. 4. Laboratories–standards. 5. Quality Control. QV 744 H877v 2007]
QD75.4.Q34H83 2007
543.068'5–dc22

2007020360

Preface

Validation and qualification of analytical methods and equipment are required by many regulations, regulatory guidance documents, quality standards, and company policies. If executed correctly, they also help to improve the reliability, consistency, and accuracy of analytical data. This book, *Validation and Qualification in Analytical Laboratories*, guides analysts, laboratory managers, quality assurance managers, and validation professionals through the validation and qualification processes in analytical laboratories.

The validation and qualification procedures presented in this book help to ensure compliance and quality, but with minimal extra cost and administrative complexity. Its purpose is to answer the key question regarding validation: How much validation is needed and how much is sufficient? The recommendations are complementary rather than contradictory to any regulations, standards, or official guidelines. They are based mainly on common sense and can be used in cases where information from official guidelines and standards is insufficient for day-to-day work.

This book addresses both international and national regulations and quality standards. Its concept, examples, templates, and operating procedures are based on my more than twenty years of multinational experience, and incorporate all aspects of validation and qualification in use at the top companies in these fields. Input has also been taken from personal discussions with regulatory agencies, managers, and chemists at laboratories, and from corporate quality assurance managers, quality control managers, and vendors of equipment and chemicals. Readers of this book will learn how to speed up their validation and qualification processes, thereby avoiding troublesome—and costly—reworking, and gaining confidence for audits and inspections.

Readers of the best-selling first edition of this title told me that they especially liked the practical common-sense approach supported with bulleted lists, checklists, templates, and standard operating procedures with step-by-step instructions. In this new edition, I have incorporated and further elaborated on this concept. For example, I have added templates with examples

for an equipment master list, for a validation master plan, and for testing of computer systems. Such tools will help readers to better understand and easily implement qualification and validation projects.

Aside from updating the core content of the first edition, creating this revision also provided me with the opportunity to address topics that are new and burgeoning in the field. Examples include risk management and validation of functionality as required by the FDA's 21 CFR Part 11. Risk management has been recommended by regulatory agencies and will help to focus resources on processes that have a high impact on product quality and data integrity. If implemented properly, this will improve the quality of high-impact products and reduce costs. Savings come from spending little or no time on processes that have a low impact on product quality.

In the chapter on validation of computerized systems, we have added recommendations for validation of functionality as required by the FDA's regulation for electronic records and signatures, 21 CFR Part 11. This takes into account that more and more records are generated, maintained, and archived on computer systems.

I have also added a new chapter on managing out-of-specification test results and failure investigations. Proper handling of deviations from product specifications with corrective and preventive action plans is an increasing concern of healthcare agencies. It avoids the possibility of products entering the market that are unsafe due to high amounts of harmful impurities. This chapter is also important due to the fact that probably more than 30% of all FDA inspection reports show inadequate handling of out-of-specification test results.

This book is intended to help clarify certain current issues in the area of validation and qualification in analytical laboratories. Readers are encouraged to submit their comments and suggestions, especially if their experiences have been different in daily laboratory work. Comments should be submitted to the LabCompliance Web site at www.labcompliance.com.

Ludwig Huber

Contents

1

Introduction

The purpose of any chemical analytical measurement is to get consistent, reliable, and accurate data. There is no doubt that incorrect measurement results can lead to tremendous costs, for example:

- If a product with incorrectly measured specifications is marketed, it may have to be recalled.
- If drugs with undetected impurities are distributed, they can have a negative impact on peoples' health.
- If harmful contaminants in environmental or food samples are not detected, they can be dangerous to the environment or to consumers.

In addition, reporting incorrect analytical results at any particular time leads to loss of a laboratory's confidence in the validity of future results. Therefore, any laboratory should do its utmost to ensure measuring and reporting reliable and accurate data within a known level of confidence. Validation and qualification of processes and equipment will help to meet this goal.

There is a second aspect to the importance of validation and qualification, which is equally important for those working in a regulated or accredited environment. Even though validation and qualification are frequently not directly spelled out in regulations and official guidelines, such as Good Laboratory Practice (GLP) and Good Manufacturing Practice (GMP), or in accreditation standards, such as the International Organization for Standardization (ISO) standard 17025, they are usually required. This is confirmed by typical statements such as this one that appears in the U.S. cGMP (current Good Manufacturing Practice) regulations (1): "Equipment shall be routinely calibrated, inspected and checked according to a written program to ensure proper performance." Because of their direct impact on product quality and consumer safety, analytical test results in pharmaceutical quality control are considered high-risk records and are frequently targets of inspections by the

U.S. Food and Drug Administration (FDA) and other agencies. Failing such regulatory inspections can have an immense impact on a company; for example, in the pharmaceutical industry, marketing of new products may be delayed and shipment of existing products may be discontinued.

Because of their importance, all kinds of validation issues have been addressed by several public and private organizations:

- The FDA has published industry guides on analytical procedures and methods validation (2) and bioanalytical method validation (3).
- The International Conference for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) has published two guidelines on the validation of analytical procedures (4,5).
- The U.S. Pharmacopeia (USP) has published a draft chapter on analytical instrument qualification (6).
- International Society for Pharmaceutical Engineering (ISPE) has published a good practices guide on the validation of laboratory systems (7).
- The U.S. Environmental Protection Agency (EPA) has developed the handbook titled "Guidance for Methods Development and Methods Validation for the Resource Conservation and Recovery Act (RCRA) Program (8)."
- The Association of Official Analytical Chemists (AOAC) has as its primary objectives the development and publication of analytical methods for substances affecting public health and safety and economic protection of the consumer or quality of environment. The organization has published guidelines on method validation as part of their peer-verified methods program (9) manual.
- ISO has developed guides on control charts (10–13) for data validation and on the qualification of reference material (14–16).
- The European Union (EU) has published Annex 15 to the EU Guide to Good Manufacturing Practice: Validation and Qualification (17).

Validation is an old concept in analytical laboratories. Good scientists have always validated analytical methods before using them for routine analysis, and equipment has been tested before it has been used for measurements. Therefore, the reader may ask, "Why is there a need for such a book at all?" In today's analytical laboratories, there are many problems with validation and qualification. Some of these problems are as follows:

1. Frequently, there is a lack of documented procedures and documented validation results. Analysts have often told the author that their methods and equipment have been validated, but when asked

for reference plots or for the exact procedure they used, there was no documentation available. The subject of compliance has brought about this major change: the need for documenting procedures and the validation results.

2. Only part of the total analytical procedure has been validated but not the complete procedure. For example, frequently the analysis step itself has been validated but not the sampling, sample transfer, or sample preparation steps, which very often contribute most to an overall error (Fig. 1).
3. Accessories and materials used for equipment qualification are not qualified. For example, there is no quality assurance (QA) program for chemical standards used to calibrate the equipment.
4. Procedures, performance parameters, and acceptance limits for the operational qualification (OQ) of equipment hardware are not known.
5. There is a lot of uncertainty about procedures and the frequency of software and computer system validation.
6. Today, most laboratories have networks installed that support regulated applications. Information technology (IT) professionals and external service providers supporting these networks may not be familiar with FDA Regulations and there are no procedures to qualify the network.
7. Frequently, qualification and validation are done at just one particular point in time. A method is validated at the end of development, and equipment is qualified to meet specifications at the time of installation. However, validation and qualification are an ongoing process and cover the complete life of methods or equipment. Equipment qualification begins when laboratories have a need for new equipment and define specifications; it ends when the equipment is taken out of service (Fig. 2).
8. Validation of analytical equipment and computer systems is not based on risk of the equipment on product quality. Frequently this results in too much testing of medium- and low-risk processes and systems.
9. There is a lot of information and assistance on the qualification of newly purchased systems. However, users of existing equipment are unsure if the same criteria should be used for the qualification of existing systems.

This book is intended to help readers find answers to these problems. Recommendations made in the book reflect the author's common sense and are based on practical experience. References to official guidelines and standards are given where appropriate.

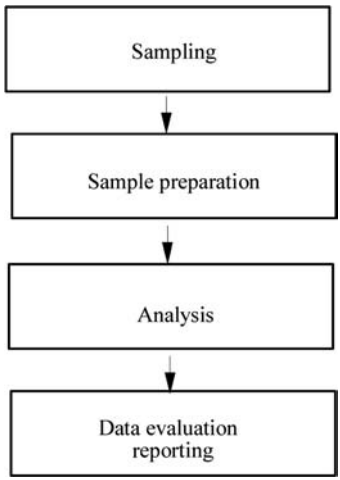


Figure 1 Validation activities include the complete analytical procedure.

This book covers all practical aspects of validation and qualification in analytical laboratories (Fig. 3). The chapter on regulations, quality standards, and related guidelines is followed by terminology and an overview of the validation and planning steps. Chapter 4 discusses risk assessment and management for laboratory systems. This has been added in response to the FDA's twenty-first-century drug cGMP initiative. The key point of this initiative is to focus compliance and validation efforts toward high-risk processes and systems. The next five chapters discuss the qualification of equipment, hardware, and software, from design qualification (DQ) and installation qualification (IQ) to operational (OQ) and performance qualification (PQ).

Chapters 11 through 14 are dedicated to the validation and qualification of methods and data, handling out-of-specifications (OOS), and reference compounds. The chapter on OOS has been added after the FDA released the final guidance on investigating OOS test results for pharmaceutical production. The final three chapters discuss the qualifications of people, proficiency testing for external quality control, and audits.

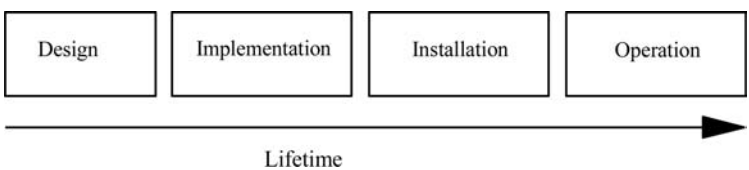


Figure 2 Equipment qualification covers the complete lifetime of equipment.

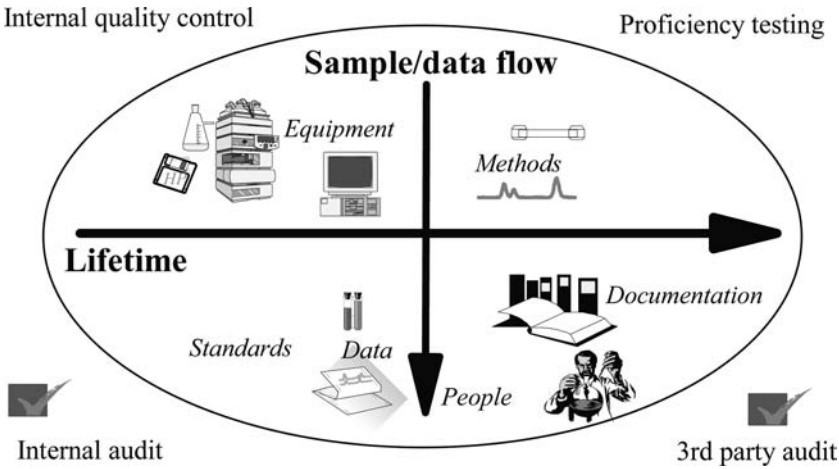


Figure 3 Validation and qualification in analytical laboratories covers all steps in the sample and data flow. It includes procedures, people, documentation and methods, and equipment throughout the entire lifetime.

The appendices include practical examples and procedures for validation and qualification, such as standard operating procedures for validation of analytical methods and equipment.

Even though this book uses chromatography as the primary example, the concepts and strategies can be applied to the validation of other analytical techniques and equipment as well. The author has tried to cover as many aspects as possible and has made reference to the relevant quality standards and regulations in the individual chapters. This does not mean that all recommendations should be followed for every situation. Readers should carefully evaluate whether or not recommendations made in the book are appropriate for their work. Conclusions of the evaluation and their implementation in a laboratory should be part of an overall quality system and justified and documented in a quality manual or in a laboratory compliance master plan.

Regulations and quality standards, as well as related guidelines, are not specific enough and leave a lot of room for analysts, inspectors, and auditors. Certain questions should always be asked, such as the size of the impact if the system fails or generates inaccurate analytical results due to lacking or insufficient validation, and the likelihood that a system will fail. The extent of validation should be based on the compliance and business risk of the data generated by the system. If there is any doubt, the final answer can be obtained only by asking if the qualification or validation effort adds any scientific value, or compliance and business value. One should never forget that the primary goal of any analyst is to generate and deliver analysis data that are scientifically sound, whether they are submitted to a regulatory agency as part of a new drug application or delivered to a company's internal or external client.

Well-designed, developed, and validated analytical methods, equipment, and materials, together with motivated and qualified people, are prerequisites to achieve this goal and are part of good analytical practice.

The challenge for any validation plan is to find the optimal validation effort that is somewhere between doing nothing and the attempt to validate everything 100%. For example, the author has experienced these two extremes with the validation of commercial standard software for chromatographic instrument control and data evaluation. Some users felt they had to do nothing in the laboratory; others went to the full check of each function, which took several months, even when this had already been done at the vendor's site.

The principle is quite clear and is illustrated in Figure 4. Costs for validation increase when going from no validation to 100%. Full validation for a commercial off-the-shelf system would mean, for example, testing each function of the software under a normal versus a high load across and beyond the expected application range, and applying this testing to each possible system configuration. In addition, whenever the system is changed, whether computer hardware, operating system, or application software, full revalidation would require the same tests again. In today's rapidly changing computer environment this would mean that the system is used 100% for testing.

The optimum is somewhere in between zero and 100% and the range depends on the impact the software or system has on (drug) product quality. For example, a system used in early drug development stages will have a lower direct impact and require less validation than a system used in pharmaceutical quality control.

The optimization process is illustrated in Figure 4. When done at the beginning of the validation process, the additional value of each validation step is tremendous. However, when trying to validate everything, the additional value goes to zero. On the other hand, the incremental costs for validation

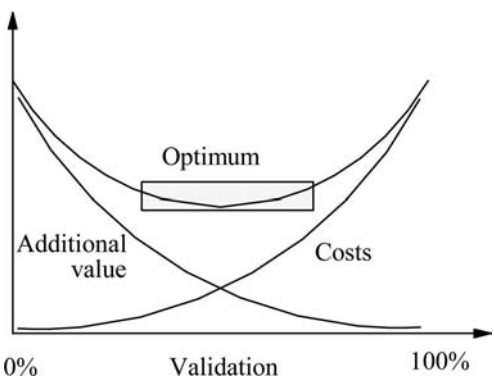


Figure 4 Optimization of validation, additional value, and cost vs. completeness of validation.

go up with any validation effort. The question is: "Where is the optimum?" or "How much validation is enough?" The challenge is to find the optimum. The hope is that, with the help of this book, and the information in Chapter 4 on risk-based validation in particular, the reader will have an appropriate guide to finding this optimum for a specific process, which depends on the complexity of the process or system and the risk the system has on product quality and finally on consumer safety.

2

Regulations, Standards, and Guidelines

What Is Discussed in this Chapter?

1. Regulations and official guidelines that are important for analytical laboratories (e.g., GLP, cGMP, ICH, USP)
2. Quality and accreditation standards and related guidance documents that are important for analytical laboratories. (e.g., ISO (International Organization for Standardisation), EURACHEM)
3. The key contents of regulations, official guidelines, and quality standards regarding validation and qualification
4. Guidance documents from industry task forces that are available for interpreting the regulations and official guidelines (e.g., GAMP)
5. Textbooks and other important publications that are available from experts

All regulations and quality standards that are applied in analytical laboratories include one or more sections with explicit or implicit requirements on validation, verification, or qualification of reference material, equipment, methods, or procedures. Their general requirement is "suitability for intended use," which means, in practice, qualified or validated to meet previously specified requirements.

Legislation is one of two major forces driving validation and qualification in analytical laboratories. The second and more important reason for validation and qualification is to improve analytical results. It has always been an objective of good analytical scientists to meet this second goal, and, in this respect, validation and qualification are nothing new in analytical laboratories. In every case, a good scientist should have checked his or her equipment for performance level and should have validated analytical methods and procedures before using them routinely. Although most individuals have been qualified for their jobs, documented procedures have frequently not

been followed, and results have not been accurately documented. These two important points are invariably reviewed by regulatory inspectors and quality standard auditors.

If validation and qualification are not performed according to regulations and guidelines, laboratories will fail to pass inspections or audits with significant financial impact. Therefore, regulatory requirements and quality standards play a major role in all validation and qualification issues, and everyone working in regulated or quality standards environments should be familiar with their requirements. This entire chapter has been dedicated to regulations and standards because of their importance and impact on analytical laboratories. The most significant regulations and guidance documents are also described in an overview. Certain specific requirements are discussed in more detail in consecutive sections.

OVERVIEW

The most important regulations applying to validations are the good manufacturing practices (GMPs), good clinical practices (GCPs), and good laboratory practices (GLPs). The best-known quality standards are the ISO 9000 series, which provide generic standards for development, manufacturing, and service. The most frequently used quality and accreditation standard in chemical testing laboratories is the ISO 17025 Standard.

When the first regulations were released, there was little guidance for chemists in analytical laboratories on how to apply these regulations to analytical equipment and procedures. Regulations often include inexplicit sentences, such as "equipment should be of appropriate design and adequate capacity and shall be adequately tested and calibrated." Laboratory chemists have been uncertain about exactly what the words appropriate design and capacity or adequate testing and calibration mean in practice. It was usual for chemists to perform a particular task and for internal and external auditors to come in and instruct them to do further or different tests and to prepare additional documentation. This often occurred without being backed up by any specific scientific reasons. Lab managers and chemists were asked to satisfy all the inspectors' requirements in order to be absolutely certain to pass the next audit. For example, Sharp (18) reported a case where he had asked a senior technician in a major British company if he would accede to any U.S. FDA request or suggestion, no matter how unreasonable or absurd it was. The technician replied, "We would not argue. We would just do it. The U.S. market is too big to lose."

Validation and qualification practices are more strongly driven by the level of enforcement across industries and countries than by any noticeable differences in regulations. It is the author's experience that the highest enforcement level in industry can be seen in pharmaceutical manufacturing and contract organizations supporting pharmaceutical manufacturing, followed by

pharmaceutical development. From a geographical point of view, the highest enforcement level is found in the United States, Canada, and Europe followed by Australia, Japan, and other countries in Asia.

Dealing with different regulatory expectations is an unsatisfactory situation and leaves a lot of room for uncertainty. One question that has frequently arisen is: "How much validation is enough?" The real problem lies in the lack of clear guidelines on how to implement regulations and quality standards. What kind of testing and how much testing is required are left very open to the interpretation of the internal and external auditors.

This situation is changing somewhat. The increasing globalization of pharmaceutical development and manufacturing has resulted in cross-geography inspections and has increased the awareness for validation and compliance in those countries that previously did not pay much attention. In addition, regulatory agencies and task forces have developed inspection guides and other guidance documents that are now available to the public.

Most promising in this area is the Pharmaceutical Inspection Co-operation Scheme (PIC/S). Its mission is "To lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products. This is to be achieved by developing and promoting harmonised GMP standards and guidance documents; training competent authorities, in particular inspectors; assessing (and reassessing) inspectorates; and facilitating the co-operation and networking for competent authorities and international organizations." At this writing, in 2007, the organization includes members from 29 countries with more on the waiting list. Member countries are from Europe, Canada, Australia, Singapore, and Malaysia. The U.S. FDA has applied for membership and intends to join in 2008.

Some examples for documents that are useful in preparation for inspections are:

- the PIC/S inspection guides for quality control laboratories (19) and for biotechnology manufacturers (20) and the guide for inspectors on using computers in GxP environments (21);
- the FDA Inspection guides for pharmaceutical quality control laboratories (22), the biotechnology inspection guide (23) the foreign inspection guide (24), and the drug manufacturer inspection guide (25); and
- the FDA industry guides on Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production and (26) and Quality Systems Approach to Pharmaceutical CGMP Regulations (27).

The U.S. FDA and PIC/S make most of these guidance documents available to the public through the Internet at www.fda.gov/cder/guidance/index.htm and www.picsheme.org.

Private organizations, sometimes funded by the public, have developed guidance documents on selected topics. Examples are given below:

- The USP has developed guidelines on validation of analytical methods and system suitability testing (28).
- A special interest group of GAMP has developed a good practices guide for validation of laboratory computer systems (7).
- The U.K. Pharmaceutical Analysis Science Group (PASG) has developed a position paper on equipment qualification for pharmaceutical laboratories (29).
- The U.K. Laboratory of the Government Chemist (LGC) and EURACHEM have developed guidance documents on equipment qualification of analytical instruments (29).
- The Co-operation on International Traceability in Analytical Chemistry (CITAC) and EURACHEM have developed an international guide to quality in analytical chemistry (31).
- The ICH has developed guidance documents for the validation of analytical procedures and other topics (4,5).

This chapter discusses in detail the content of these regulations and quality standards and related guidelines regarding validation and qualification in analytical laboratories.

SPECIFIC REGULATIONS AND GUIDELINES

Good Laboratory Practice

GLP regulations for assuring the validity of toxicological studies were first proposed by the U.S. FDA in November 1976, and final regulations were codified as Part 58 of Chapter 21 of the Code of Federal Regulations in 1979 (32). For safety testing of agricultural and industrial chemicals under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) (33) and the Toxic Substance Control Act (TSCA) (34), respectively, the EPA issued almost identical regulations in 1983 to cover required health and safety aspects. The Organization for Economic Cooperation and Development (OECD) published the principles in *Good Laboratory Practice in the Testing of Chemicals* (35) in 1982, which has since been updated (36) and incorporated by OECD member countries into their own legislation. In Europe, the European Union (EU), formerly the European Community (EC), has made efforts to harmonize laws through the council directives in *The Harmonization of Laws, Regulations*

and Administrative Provisions to the Application of the Principles of Good Laboratory Practice and the Verification of Their Application for Tests on Chemical Substances (2004) (37) and *The Inspection and Verification of Good Laboratory Practice* (1988, last adopted in 2004) (38). This directive makes provision for a verification procedure for laboratories claiming to use GLP in conducting tests on chemicals.

All GLP regulations include chapters on equipment design and maintenance, for example, U.S. GLP regulations, Sections 58.61 and 58.63 (32):

- Automatic, mechanical, or electronic equipment used in the generation, measurement, or assessment of data shall be of appropriate design and adequate capacity to function according to the protocol and shall be suitably located for operation, inspection, cleaning, and maintenance.
- Equipment used for generation, measurement, or assessment of data shall be adequately tested, calibrated, and/or standardized.
- Written standard operating procedures shall set forth in sufficient detail the methods, materials, and schedules to be used in routine inspection, cleaning, maintenance, testing, calibration, and/or standardization of equipment and shall specify remedial action to be taken in the event of failure or malfunction of equipment.
- Written records shall be maintained of all inspection operations.

The GLP principles of the OECD include similar but shorter sections on equipment (36):

- The apparatus used for the generation of data and for controlling environmental factors relevant to the study should be suitably located and of appropriate design and adequate capacity.
- Apparatus and materials used in a study should be periodically inspected, cleaned, maintained, and calibrated according to Standard Operating Procedures. Records of procedures should be maintained.

Current Good Manufacturing Practice Regulations

GMP regulates manufacturing and its associated quality control (in contrast to GLP, which mainly covers drug development activities). GMP predates GLP. Industries were already familiar with GMP and thus GLP takes a similar line; the most significant difference is in archiving requirements for test samples and data.

GMP regulations have been developed to ensure that medicinal (pharmaceutical) products are consistently produced and controlled according to the quality standards appropriate to their intended use. In the United States, the regulations are called Current Good Manufacturing Practices (cGMP) to account for the fact that the regulations are dynamic rather than static. 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* (1). Drugs marketed in the United States must first receive FDA approval and must be manufactured in accordance with the U.S. cGMP regulations. Because of this, FDA regulations have set an international regulation benchmark for pharmaceutical manufacturing.

In Europe, local GMP regulations exist in many countries. These are based on the EU directive: *Good Manufacturing Practice for Medicinal Products in the European Community* (39). This EU GMP directive is necessary to permit free trade in medicinal products between the member countries. Regulations in the EU allow the marketing of a new drug in the member countries with the acquisition of just a single marketing approval. The intention of the EU GMP is to establish a minimum manufacturing standard for all member countries.

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) (40). For example, Switzerland, a non-EU member country, has adopted the PIC guide as the national GMP regulation.

GMP is concerned with both production and quality control (QC). The basic requirements of QC are as follows:

- The Quality Control Unit is established that is responsible to reject or approve all components, drug product containers, packaging material, drug products, to review production records, and to approve or reject procedures and processes, e.g., validation, labeling, process control.
- No batch of a product is released for sale or supply prior to certification by an authorized person to confirm that it is in accordance with the requirements of the marketing.
- 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 QC.

- Equipment has the appropriate design and adequate size and is suitably located for intended use and for cleaning and maintenance.
- Equipment, including automated equipment and computer systems, is calibrated or otherwise qualified or validated for intended use.
- Test methods are validated.
- Records are made manually and/or by recording instruments that demonstrate that all required sampling, inspecting, and testing procedures were actually carried out. Any deviations are fully recorded and investigated.
- Procedures are available for production and process control. The procedures are drafted and approved by organizational unit and approved by quality control unit.
- 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 demonstrate that testing of materials and intermediate, bulk, and finished products is formally assessed against specification. Product assessment includes a review and production documentation relevant to evaluation and an assessment of deviations from specified procedures.
- Sufficient reference samples of starting materials products are retained to permit future examination of the product if necessary so that the product can be retained in its final pack, unless exceptionally large packs are produced.

The U.S. FDA published a *Guide to Inspection of Pharmaceutical Quality Control Laboratories* (22). Even though it was written as a guideline for field investigators, it is a useful document for QC laboratories. It includes extensive chapters on the handling of Out of Specification (OOS) laboratory test results and on retesting. Additional chapters provide guidelines on laboratory records and documentation, laboratory standards solutions, methods validation, equipment, raw material testing, in-process control, the computerized laboratory data acquisition system, and laboratory management.

The *EC Guide to Good Manufacturing Practice* (39) contains one short section on equipment and method validation:

- All equipment should be subject to planned maintenance and validation.
- Analytical methods should be validated.

- All testing operations described in the marketing authorization should be carried out according to the approved methods.

Annex 11 (41) and Annex 15 (17) of the EC guide have more specific information on the use of computers in the GMP environment and on validation and qualification in general.

21 CFR Part 11 for Electronic Records and Signatures

In 1997, the U.S. FDA issued a regulation that provides criteria for acceptance by the FDA of electronic records, electronic signatures, and handwritten signatures (42). This was done in response to requests from the industry. With this regulation, entitled Rule 21 CFR Part 11, electronic records can be equivalent to paper records and handwritten signatures. The rule applies to all industry segments regulated by the FDA that includes GLP, GCP, and current cGMP.

The use of electronic records is expected to be more cost-effective for the industry and the FDA. The approval process is expected to be shorter and access to documentation faster and more productive.

The primary requirements of the regulation for analytical laboratories are listed below:

- Use of validated existing and new equipment and computer systems
- Secure retention of electronic records to instantly reconstruct the analysis
- User independent computer-generated time-stamped audit trails
- 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

It is out of the scope of this book to discuss and explain how the requirements can be implemented in analytical laboratories. This has been described in a primer dedicated to this rule (43). This book will elaborate on the validation aspect of the rule.

International Conference on Harmonization Guidelines

The ICH is a unique project that brings together the regulatory authorities of Europe, Japan, and the United States, and the experts from these three regions, to discuss scientific and technical aspects of product registration (44).

The ICH has three purposes:

1. To provide a forum for a constructive dialog between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, United States, and Japan. Members come from industry and regulatory agencies.
2. To identify areas where modifications in technical requirements, or greater mutual acceptance of research and development procedures, could lead to a more economical use of human, animal, and material resources without compromising safety.
3. To make recommendations on practical ways to achieve greater harmonization in the interpretation and applications of technical requirements for registration.

The ICH publishes the results as guidelines to regulatory authorities and to industry professionals in the member countries. The member countries ultimately sign off on the guidelines to produce regulations. The most important guidelines related to the topic of this book are those for the validation of analytical methods, stability testing, impurity testing, good manufacturing of APIs, and risk assessment:

- Q2A: Validation of analytical procedures (4), with a list of performance criteria for method validation and definition of the terminology
- Q2B: Validation of analytical procedures: methodology (5) with recommendations on how to measure and evaluate some of the parameters
- Q4B: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC) (45)
- Q1A(R2): Stability Testing of New Drug Substances and Products (Second Revision) (46)
- Q3A(R2): Impurities in New Drug Substances (Revised Guideline) (47)
- Q3B(R2): Impurities in New Drug Products (Revised Guideline) (48)
- Q7: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients (49)
- Q9: Quality Risk Management (50)

The most specific guide is Q7A on GMPs for APIs. Requirements are similar to cGMPs as published by the U.S. FDA but the ICH guide includes more details.

U.S. Pharmacopeia

The USP is the official compendium recognized by the U.S. Federal Food, Drug, and Cosmetic Act. It serves as the basis for enforcement actions by the U.S. FDA, involving official (USP) drugs, and also provides guidelines during foreign inspections. It contains chapters on the validation of analytical methods and system suitability testing (28,51). Most interesting, related to the topic of this book, is a draft chapter on Analytical Instrument Qualification (6). The approach is based on the 4Q qualification model, and the chapter includes recommendations for design qualification, installation qualification, operational qualification, and performance qualification.

SPECIFIC QUALITY STANDARDS AND GUIDELINES

Most chemical analytical laboratories already possess, or are in the process of implementing, a quality management system to maintain or improve the quality, consistency, and reliability of data. A documented quality system is also a prerequisite for obtaining accreditation or for registering to a quality standard such as the ISO 9000 Compendium.

ISO 9000 Standards Family

ISO is a network of the national standards institutes of 157 countries, on the basis of one member per country, with a Central Secretariat in Geneva, Switzerland, that coordinates the system. Probably the most well known ISO publication is the ISO 9000 Standards Quality Management Compendium (52). It gathers in one volume the 11 published standards and technical reports making up the ISO 9000 family. These include ISO 9001:2000, which replaces the 1994 versions of ISO 9001, ISO 9002, and ISO 9003 as the only certification standard in the family. The draft standard ISO/DIS 10018 giving guidelines on complaints handling is also included. The ISO 9000 family covers the requirements for a generic quality system in a two-party contradictory situation with an assessment made by a third party. The standards are not specific to laboratory work.

ISO/IEC 17025

Most relevant ISO Standard for laboratories is ISO/IEC 17025 (53). The standard specifies the general requirements for the competence to carry out tests and/or calibrations, including sampling. It covers testing and calibration performed using standard methods, non-standard methods, and laboratory developed methods.

The standard has replaced ISO Guide 25 (*General Requirements for the Competence of Calibration and Testing Laboratories*) and EN45001 (*Criteria for the Operation of Testing Laboratories*) as guides in establishing quality

systems in chemical testing laboratories. The standard is used as a basis for laboratory accreditation.

The standard is widely used in environmental, food, chemical, and clinical testing laboratories. The U.S. FDA and most equivalent international agencies do not mandate compliance with ISO 17025, and ISO 17025 accreditation is not sufficient for GxP compliance. Therefore, pharmaceutical laboratories stay away from getting official ISO 17025 accreditation status but many of the concepts are similar to GxP requirements.

ISO 17025 has many requirements related to the subject of this book. Laboratory-related requirements are similar to GxP requirements but include more details. They are segmented into management and technical requirements:

Management requirements

- Organization
- Document control
- Subcontracting of tests and calibrations
- Control of non-conforming testing and/or calibration work
- Corrective and preventive action
- Control of records
- Internal audits

Technical requirements

- Personnel
- Method validation
- Estimation and reporting of measurement uncertainty
- Control of data, e.g., calculations and data transfer, integrity of data
- Equipment calibration and qualification and computer system validation, safe handling and transport
- Assuring the quality of test and calibration results
- Sampling, e.g., sampling plan, sampling procedures, sample identification
- Handling of test and calibration items
- Reporting the test results

GUIDANCE DOCUMENTS OF NATIONAL AND INTERNATIONAL ORGANIZATIONS

Most national standard, accreditation or certification bodies issue guidance notes in support of their standards. For example, in the United Kingdom, the National Measurement and Accreditation System (NAMAS), now

United Kingdom Accreditation Service (UKAS), has published more than 100 such documents, many of which relate to chemical testing. Complete lists and ordering details are generally available on request from various bodies.

The U.K. Pharmaceutical Analytical Sciences Group

The PASG is a forum for analytical scientists engaged in the management and practice of analytical science in chemistry and pharmacy disciplines within research operating in the U.K. The PASG developed a position paper on equipment qualification, along with broad guidelines as to what each qualification step should include (29). The group introduced the terms design qualification, installation qualification, operational qualification, and performance *qualification* for equipment in analytical laboratories.

Co-operation on International Traceability in Analytical Chemistry (CITAC)

CITAC/EURACHEM devised the *International Guide to Quality in Analytical Chemistry-An Aid to Accreditation* (31) with the intent of providing laboratories with guidance on the best practice for improving the quality of the analytical operations they perform. It is comprehensive and very detailed concerning all aspects of validation and qualification of equipment. The guide has been primarily developed to assist laboratories in preparation for ISO Guide 25 accreditation and has been updated to accommodate support of 17025. It is not specific to support regulations but has many recommendations that are also required by regulations. Therefore, readers of this book are encouraged to follow these recommendations for validation and qualification.

1. All equipment used in laboratories should be of specification sufficient for the intended purpose and kept in a state of maintenance and calibration consistent with its use.
2. Equipment normally found in the chemical laboratory can be categorized as:

    a. general service equipment not used for making measurements or with minimal influence (e.g., hotplates, stirrers, nonvolumetric glassware, and glassware used for rough volume measurements such as measuring cylinders) and laboratory heating or ventilation systems;
    b. volumetric equipment (e.g., flasks, pipettes, pycnometers, burettes, etc.) and measuring instruments (e.g., hygrometers, U-tube viscosimeters, thermometers, timers, spectrometers, chromatographs, electrochemical meters, balances, etc.);

c. physical measurement standards (weights, reference thermometers); and
d. computers and data processors.

While these sections in the document are rather generic and similar to those found in other documents, the real value is contained in the appendices. For example, Appendix A includes a quality audit checklist with areas of particular importance in a chemical laboratory. There are checklist items on equipment, methods, and QC:

Equipment

- The equipment in use is suited to its purpose.
- Major instruments are correctly maintained and records of this maintenance are kept.
- Appropriate instructions for the use of equipment are available.
- Traceable equipment (e.g., balances, thermometers, glassware, timepieces, pipettes, etc.) are appropriately calibrated, and the corresponding certificates or other records demonstrating traceability to national measurement standards are available.
- Calibrated equipment is appropriately labeled or otherwise identified to ensure that it is not confused with uncalibrated equipment and to ensure that its calibration status is clear to the user.
- Instrument calibration procedures and performance checks are documented and available to users.
- Instrument performance checks and calibration procedures are carried out at appropriate intervals and show that calibration is maintained and day-to-day performance is acceptable. Appropriate corrective action is taken where necessary.
- Records of calibration performance checks and corrective action are maintained.

Methods and Procedures

- In-house methods are fully documented, appropriately validated and authorized for use.
- Alterations to methods are appropriately authorized.
- Copies of published and official methods are available.
- The most up-to-date version of the method is available to the analyst.
- Analyses (are observed to) follow the methods specified.
- Methods have an appropriate level of advice on calibration and quality control.

Quality Control

- There is an appropriate level of quality control for each test.
- Where control charts are used, performance has been maintained within acceptable criteria.
- QC check samples are being tested by the defined procedures at the required frequency, and there is an up-to-date record of the results and actions taken where results have exceeded action limits.
- Results from the random re-analysis of samples show an acceptable measure of agreement with the original analyses.
- Where appropriate, performance in proficiency testing schemes and/or in interlaboratory comparisons is satisfactory and has not highlighted any problems or potential problems. Where performance has been unsatisfactory, corrective action has been taken.

Appendix B gives guidance on the performance checks and calibration intervals of equipment most commonly used in analytical laboratories. These include balances, hydrometers, barometers, timers, thermometers, gas chromatographs, liquid chromatographs, and spectrometers.

Laboratory of the Government Chemist/EURACHEM-UK

The Laboratory of the Government Chemist (LGC) established a working group, under the auspices of EURACHEM-UK that developed a detailed guidance on equipment qualification. The group defined the individual qualification terms and gave recommendations on what should be included in each qualification. The guidance has been published with comments by Bedson and Sargent (30). The qualification terms as defined in the guide are used throughout this book. The same group also developed and published an even more specific guideline on the qualification of liquid chromatographs (54).

ADVICE FROM EXPERTS

Because of the lack of detailed information from regulatory agencies and other official organizations, individual experts or expert groups have emerged and have published books and other literature giving guidelines on validation and qualification. Appendix D of this book includes a bibliography of more than 30 books with titles, keywords, and ordering information. The internet is also a valuable resource to information on validation and compliance. For example,

www.labcompliance.com provides free articles for download and many links to regulations and guidance documents.

HOW TO DEAL WITH MULTIPLE REGULATIONS AND QUALITY STANDARDS

Laboratories are frequently faced with a situation where they have to comply with regulations from different countries or with both regulations and quality standards at the same time. Examples are as follows:

- A pharmaceutical company markets a drug in different countries. Manufacturing and quality laboratories has to comply with the cGMP of all countries. In this case, the analytical control laboratory also has to work in compliance with the GMPs of the countries in which the drug is marketed.
- A chemical company is certified for ISO 9001. The scope of the certification also covers the analytical service laboratory. In addition, the laboratory performs contract analyses for other companies and has received laboratory accreditation in compliance with ISO 17025. The laboratory has to work in compliance with ISO 9001 and with ISO Guide 17025.
- An independent test laboratory performs GLP studies as a subcontractor for a pharmaceutical company. Occasionally, the laboratory also performs analyses for pharmaceutical manufacturing control departments. The laboratory has also received laboratory accreditation for specific food analyses according to ISO 17025. The laboratory has to comply with ISO 17025 and with GLP and cGMP regulations.

International companies frequently face this kind of problem. Their laboratories not only have to comply with regulations from different countries but also, simultaneously, with quality and accreditation standards. The solution to this problem is to combine all regulations and quality standards in a single quality manual and a single set of operating procedures. The recommended documents and how they relate to each other are shown in Figure 1. The quality manual should place the company's own quality system first and foremost. This may be based on a well-known quality standard, such as ISO 9001 or ISO 17025. The quality manual and operating procedures should include aspects of various regulations and quality standards applied within the company. For specific regulations, such as GLPs, it should include sections that apply only to those particular regulations. For example, it might mention that if the analysis is to be done for a GLP study, raw data must be archived for the required archiving period. For a non-GLP type of analysis, such long archiving is not usually required.

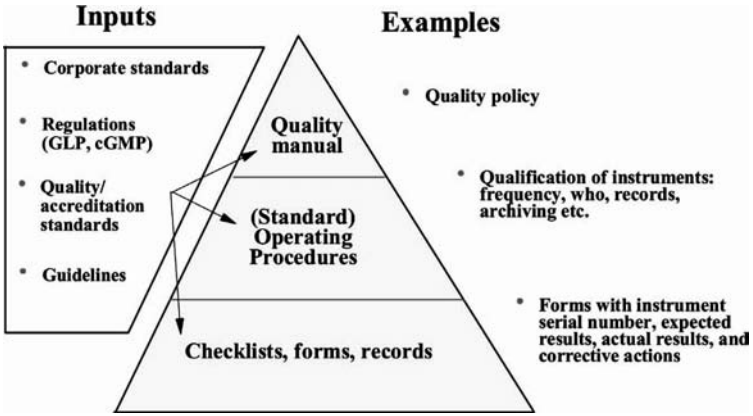


Figure 1 Quality pyramid of a system for multiple regulations and quality standards.

Summary Recommendations

1. Check to determine which regulations and quality standards apply to your laboratory.
2. Try to procure inspection, policy and interpretation guides that are relevant to your laboratory.
3. Develop a quality manual for your entity that covers all regulations, quality standards and guidelines that are relevant to your laboratory.
4. Develop operating procedures and work instructions to cover all routine operations.

3

Terminology and Validation Overview

What Is Discussed in this Chapter?

1. The difference between validation, verification, qualification, and calibration
2. Other definitions related to validation
3. The elements required for a complete qualification and validation
4. The equipment qualification process
5. Qualification deliverables for different phases
6. How to develop and implement an overall validation strategy for a laboratory

An agreement on terminology is of utmost importance for a common understanding of validation and qualification. The author has frequently noted at validation symposia that different speakers used different terms for the same thing and the same terms for different things. Consequently, discussions would start on the topic of terminology that not only wasted valuable symposium time but also left some uncertainty, because official definitions were usually not readily available for clarification, and the speakers could not reach a consensus.

The main problem is that guidelines on validation and qualification have been developed by different organizations, for different applications, at different times, and in different countries. For example, the pharmaceutical industry uses the term *equipment operational qualification* while the "ISO World" uses the term *performance verification* for confirming an instrument's compliance with previously defined specifications. Frequently, the terms *validation* and *verification* or *validation* and *qualification* are used interchangeably.

This chapter elaborates on terms most frequently used in the area of validation and qualification in analytical laboratories. Whenever available, official terms are used together with a reference to the source.

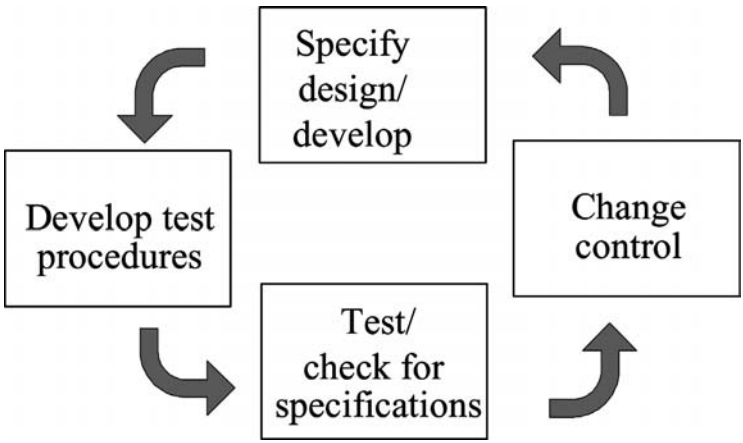


Figure 1 Principle of qualification and validation. *Source*: Ref. 55.

DEFINITIONS

The term *validation* has been defined by many different authors. Although the wording may be different, the sense is always the same: (a) specify and implement, (b) test if the specifications are met, and (c) document. One of today's commonly accepted definitions of validation can be found in the FDA's 1987 guideline, *General Principles of Validation* (56):

> *Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.*

This definition is very well thought out, and each word has a special significance. Most important in this definition are the words *documented, high degree of assurance, specific process, consistently*, and *predetermined specifications.*

The GMP guides of the EU (39), the WHO (57), and the PIC (40) have the following definition for *validation*:

> *Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, activity or system actually leads to the expected results.*

The OECD consensus document number 10 (58) defines *validation of a computerized system* as "the demonstration that a computerized system is suitable for its intended purpose."

Table 1 Key Points of Validation

Documented evidence	Validation requires thorough documentation. Everything that is not documented is considered incomplete.
High degree of assurance	The assumption is that a large software package as used in complex computerized systems is rarely free of errors. Frequently, there is a perception that validation means error-free. This assumption is wrong. During the validation process, everything realistically possible should be done to reduce errors to a high degree.
Specific process	The overall validation of software is process-, not product-, related. For example, the development and testing activities performed prior to releasing the software for manufacture are validated once for a series of products characterized by the serial number. Some subparts of validation, such as the qualifications (installation, operation, performance), are product-specific and have to be done for each system.
Consistency	Validation is not a one-time event. The performance of the equipment has to be controlled during the entire life of the product.
Predetermined specifications	Validation activities start with the definition of specifications. The performance of the equipment is then verified against these specifications. Acceptance criteria must be defined prior to testing.

Many laboratory managers associate validation with increased workload in the laboratory, through additional testing for example, but validation is essentially nothing new. Ever since the development of analytical instrumentation and methods, statistics have been used to prove the proper functioning, reliability, and precision of the equipment and methods. Firms followed software development standards and used the software development life cycle long before regulatory agencies requested the validation of computer systems. What is new to most existing validation procedures is the disciplined planning and documentation of validation and documentation of all validation steps, including testing. This also concurs with a definition of validation by Ken Chapman (59):

> *In today's pharmaceutical industry, whether you are thinking about a computer system, a water treatment system, or a manufacturing process, validation means nothing else than well-organized, well-documented common sense.*

VALIDATION VERSUS VERIFICATION, TESTING, CALIBRATION, AND QUALIFICATION

There is still considerable misunderstanding on the differences between testing, calibration, verification, and validation. The illustration in Figure 2, together with other information in the following paragraphs, should help to clarify these differences.

Testing

Testing has been defined in ISO/IEC Guide 2 (60) as:

> *A technical operation that consists of the determination of one or more characteristics or performance of a given product, material, equipment, organism, physical phenomena, process or service according to a specified procedure.*

Instrument testing is the process of executing experiments to measure the performance characteristics following documented procedures. Examples are the measurement of the baseline noise of a detector, the precision of the injection volume of an injector, or the precision of a flow rate. Requirements for testing are test conditions and written procedures with clear instructions on how to do the tests and how to evaluate the results.

Calibration

ISO/IEC Guide 2 defines *calibration* as:

> *The set of operations which establish, under specified conditions, the relationship between values indicated by a measuring instrument or measuring system and the corresponding known values of the measurand.*

A well-known example of a device that has to be calibrated is the balance. A reference weight that is traceable to a national standard is measured and the result compared with the actual weight. An example for a calibration procedure in an analytical instrument is the measurement and adjustment of the wavelength accuracy in a high performance liquid chromatography (HPLC) UV-visible detector's optical unit. Calibration is frequently confused with testing and performance verification. The differences become quite clear when looking at the precision of the peak area in chromatography. This can be tested and verified against a previously defined specification, but it cannot be calibrated. Sometimes, accurate calibration has a direct impact on

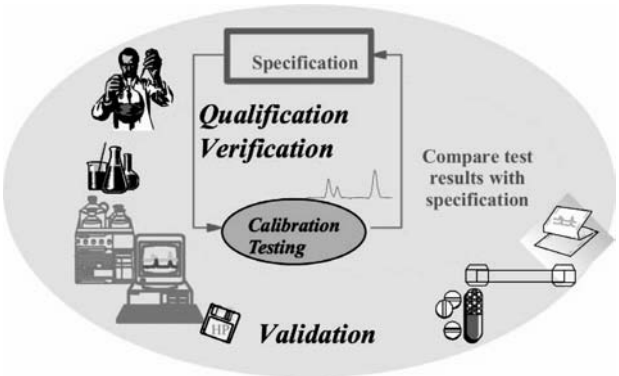


Figure 2 Testing, calibration, qualification, verification, and validation.

performance. For example, a UV detector with incorrect wavelength calibration may cause detection limits and the detector's linearity to deteriorate. The term calibration is sometimes used interchangeably with the term standardization. Calibration normally means to check against known standards, whereas standardization usually means to make uniform. For some equipment, the term calibrated is more appropriate; for other equipment, the term standardized is better. The word calibration is also frequently used in FDA regulations and inspection reports interchangeably with operational qualification of equipment.

Verification

ISO/IEC Guide 2 defines *verification* as the "confirmation by examination and provision of evidence that specified requirements have been met." Performance verification of analytical instrumentation is the process of comparing the test results with the specification. It includes testing and requires the availability of clear specifications and acceptance criteria. Examples are the same as for testing. The verification process ends with the generation and sign-off of a "Declaration of Conformity" of the instrument to specifications. Additionally, a sticker should be affixed to the instrument with the date of the last successful performance verification and the next scheduled performance verification.

Qualification

The term *qualification* has been defined by the U.S. PMA's CSVC for the installation, operation and running of a system under workload for a specific application. Like verification, qualification is also part of validation and is product-specific. The CSVC has defined three qualifications: installation, operational, and performance.

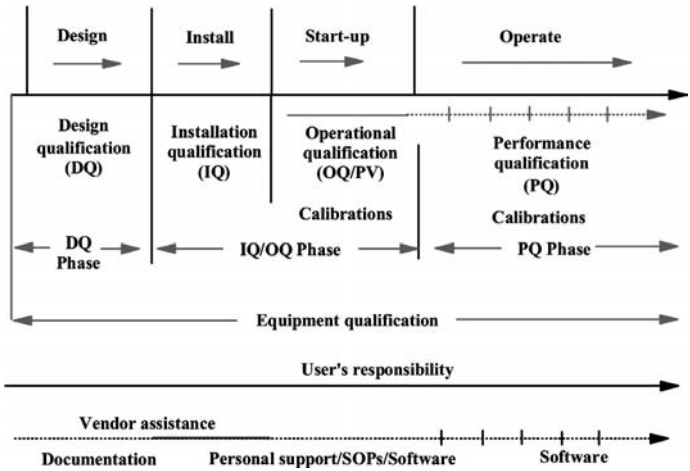


Figure 3 The qualification timeline, originally developed for the validation of a computer-controlled water treatment system, now also applies to equipment used in analytical laboratories. *Abbreviation*: SOPs, standard operating procedure.

Figure 3 illustrates the qualification timeline. It demonstrates that validation is not a one-time event but an ongoing process starting with the definition and design of the product.

Qualification also is defined, in the *EC Guide to Good Manufacturing Practice* (39), as the "action of proving that any equipment works correctly and leads to the expected results." The word *validation* is sometimes widened to incorporate the concept of qualification.

Even though the term *qualification* has been used in analytical laboratories, it was formally introduced by a workgroup of the U.K. PASG and published by M. Freeman, M. Leng, D. Morrison, and R. P. Munden. The authors applied the terms for qualification (IQ, OQ, and PQ), which were previously applied to the qualification of computer systems by the U.S. PMA, to analytical equipment. The authors also introduced the term *design qualification* (DQ).

The U.K. LGC/EURACHEM defined the individual qualification terms and gave detailed recommendations on what should be included in each qualification. The guidelines, together with some comments, have been published by Bedson and Sargent (30) and are well established in the industry.

Equipment qualification (Fig. 4) has been broken down into four parts:

1. DQ, for setting functional and performance specifications (operational specifications);

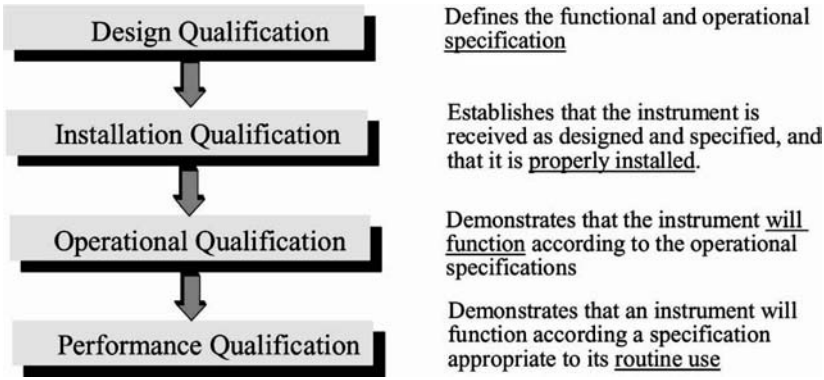


Figure 4 Equipment qualification.

2. IQ, for performing and documenting the installation in the selected user environment;
3. OQ, for testing the equipment in the selected user environment to ensure that it meets the previously defined functional and performance specifications; and
4. PQ, for testing that the system performs as intended for the selected application.

STRATEGY FOR DEVELOPMENT AND IMPLEMENTATION OF A QUALIFICATION AND VALIDATION SYSTEM IN A LABORATORY

Validation efforts in an analytical laboratory can be broken down into separate components addressing the validation/qualification of:

- equipment hardware,
- software and computer systems,
- analytical procedures and methods,
- analytical systems,
- analytical data,
- reference standards, and
- people.

The various validation activities in an analytical laboratory are illustrated in Figure 5.

Table 2 Recommended Qualification Activities for Equipment Events

	DQ	IQ	OQ	PQ
Before purchasing	Yes			
During installation		Yes		
Before operation			Yes	Yes
During operation			(2)	Yes
After hardware repair, e.g., replace GC injection port		(1)	Partial	Yes
Hardware update e.g., additional LC detector	Partial	Yes	Partial	Yes
Firmware update		Yes		Yes
Software update	(3)	Yes	(3)	Yes
Move equipment to other building		Yes	Yes	Yes
New operator				Yes
Column replacement (in chromatography)				Yes
New use of equipment (new application not previously specified)	Yes		(4)	Yes

(1) Only if the part to be exchanged has a new serial number. (2) Frequency depends on the equipment, for example, for a chromatograph it is about once per year. (3) If the update includes new functions that will be used for the user's application. (4) Yes, if new functions are used that previously had not been tested.
Abbreviations: DQ, design qualification; IQ, installation qualification; OQ, operational qualification; PQ, performance qualification.
Source: Ref. 55.

For overall validation and qualification as well as validation processes, the author recommends the following steps:

1. Develop procedures for validation and qualification.
2. Make sure that all laboratory work staff is adequately qualified through appropriate education, training or experience. Training needs should be established, and records of the staff's qualifications should be maintained.
3. Qualify tools and chemical standards for instrument calibration and QC checks following documented plans. Such qualification can include verification of the traceability of calibration tools to national standards and the amounts and purity of chemical standards. Define the intended use and specifications for equipment and analytical procedures.
4. Qualify analytical hardware at installation prior to routine use and, if necessary, after repair and at regular intervals.

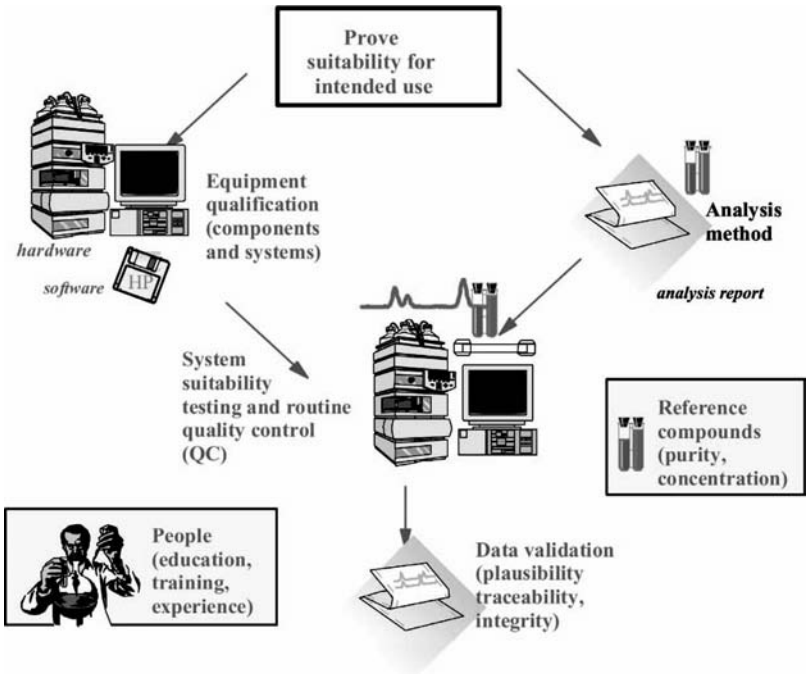


Figure 5 Validation and qualification in the analytical laboratory.

5. Validate software and computer systems during and at the end of the development process. If such systems are purchased, the vendor should be qualified.
6. Qualify software and computer systems at the time of installation in the user's laboratory prior to their routine use, at regular intervals and, if necessary, after software and hardware updates.
7. Validate analytical methods during and after development. Method validation covers definition and testing of significant method characteristics, for example, limit of detection, limit of quantitation, selectivity, linearity, and ruggedness. If the method is to be run on different instruments, it also should be validated on the different instruments as specified in the scope of the method. Only when it is clearly specified that the method will always run on the same instrument can validation efforts be limited to that instrument. Methods should be validated at the end of method development prior to routine use and whenever any method parameter has been changed.

8. Combine a specific method with specific equipment hardware, software, accessories (such as columns), and chemical standards, and test the suitability of the system for a specific analysis. This qualification, usually referred to as PQ, tests a system against documented system performance specifications for the specific analytical method. Analytical systems should be tested for ongoing performance prior to and during routine use, practically on a day-to-day basis.
9. When analyzing samples, validate the data. The validation process includes documentation and checks for data plausibility, data integrity, and traceability. The uncertainty of the measurement results should be estimated and reported together with the analytical data. A complete audit trail that allows the final result to be traced back to the raw data should be in place.
10. Verify that the entire analytical procedure is validated with well-characterized control samples that are interspersed between unknown samples. Results of control samples are compared with known amounts. If the results are within specified limits, the complete analytical procedure is validated. This process is called internal analytical QC.
11. For external analytical QC, participate in proficiency testing. Well-characterized samples with known amounts are distributed to a group of laboratories doing similar analyses. The samples are analyzed, and the results are sent back to the distributing agency. The agency evaluates the results and informs the laboratories of their performance.
12. Conduct regular internal audits to check that the laboratory's QA system is effective, documented, and adhered to by the entire staff.

The details of these steps are discussed later in this book.

Summary Recommendations

1. Develop a glossary with terms on regulations for your entity. Appendix A of this book includes an extensive glossary on all aspects of validation and qualification in analytical laboratories. This glossary can be used to develop a company-specific glossary.
2. Make sure that the definitions that you have developed for your entity are used throughout all processes, in all documents and in all departments.

3. Make sure that all employees have a copy of the definitions that you have developed for your entity readily available when they attend external meetings and conferences.
4. Develop and implement a validation and qualification strategy for your laboratory.

4

Risk-Based Validation and Qualification

What Is Discussed in this Chapter?

1. Regulations and guidelines related to risk assessment
2. Recommendations from industry task forces
3. Approaches and tools for risk assessment
4. Steps for risk assessment and management
5. Risk-based validation and qualification tasks

The efforts for validation and qualification should be balanced against the benefits, which means the amount of work should be in line with the problems that can occur if processes and systems are not fully validated. The mechanism for this is risk assessment and the definition of the extent of validation, according to the risk, that a specific process or system can have on product quality and, ultimately, consumer safety. The risk-based approach should enhance the laboratory's ability to focus on identifying and controlling critical functions that affect product quality, so that less or no time is spent on systems and functions that have little or no impact on product quality and consumer safety.

Industry task forces have recommended risk-based approaches for validation. For example, GAMP has an appendix in the guide on Validation of Automated Systems in Pharmaceutical Manufacture (61) and a chapter in the good practices guide on Validation of Laboratory Computerized Systems (6).

The U.S. FDA has also recognized the importance of risk-based compliance. This became most obvious when the FDA announced and promoted science- and risk-based approaches as part of the Twenty-first Century Drug GMP Initiative in 2003 (62).

However, the FDA not only takes advantage of risk-based approaches for their own benefit; it also encourages the industry to do the same, for

example, for software and computer validation. The industry guidance on General Principles of Software Validation states:

> *The selection of validation activities, tasks, and work items should be commensurated with the complexity of the software design and the risk associated with the use of the software for the specified intended use (63).*

The same guide has specific recommendations on what is expected for lower risk systems:

> *For lower risk devices, only baseline validation activities may be conducted. As the risk increases additional validation activities should be added to cover the additional risk.*

The Part 11 guidance on Scope and Applications (64) recommends basing the extent of validation for computer systems on a justified and documented risk assessment. The guide also gives an example where validation is not important:

> *We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity. For instance, validation would not be important for a word processor used only to generate SOPs (64).*

Specific advice for risk-based compliance of computer systems came from the Pharmaceutical Inspection Convention: Good Practices for Computerized Systems in Regulated Environments (21). It has several recommendations related to risks:

> *For critical GxP applications it is essential for the regulated user to define a requirement specification prior to selection and to carry out a properly documented risk analysis for the various system options. This risk-based approach is one way for a firm to demonstrate that they have applied a controlled methodology, to determine the degree of assurance that a computerised system is fit for purpose.*

> *The inspector will consider the potential risks, from the automated system to product/material quality or data integrity, as identified and documented by the regulated user, in order to assess the fitness for purpose of the particular system(s). The business/GxP criticality and risks relating to the application will determine the nature and extent of any assessment of suppliers and software products.*

Annex 15 of the EU GMP Directive on Validation and Qualification (15) recommends basing the scope and extent of validation on risk:

> *A risk assessment approach should be used to determine the scope and extent of validation.*

The National Institute of Information Technology has developed a guide on Risk Management for Information Technology Systems (65). The ICH has developed a guide on Quality Risk Management (50). Annex I, titled Potential Opportunities for Conducting Risk Management, has a chapter on Quality Risk Management as Part of Laboratory Control and Stability Studies.

The FDA and other agencies expect a documented risk assessment for the overall laboratory processes. This should include all sub-processes that can impact the quality of analytical results. Steps include sampling, transport, storage, preparation, analysis of samples, and evaluation and storage of data. For critical sub-processes the impact of equipment and material should also be assessed, for example, analytical equipment and computer systems.

For critical analyses, such as those in pharmaceutical quality control, laboratories are expected to assess the risks and to identify risk categories for each laboratory system, otherwise full validation is required. Companies without a justified risk assessment would not be able to defend their selection of a certain level of validation. The real value in a comprehensive risk-based validation approach is in doing exactly the right amount and detail of validation for each system.

In the past companies frequently applied the principle of this kind of risk-based validation, but the rationale behind this was not documented and the approach was not consistently implemented within a company. The extent of validation depended more on the individual validation professionals than on a structured rationale.

Laboratories have frequently made risk assessments and mitigated risks without a detailed risk management plan. For example, laboratories have spare parts such as a UV detector lamp readily available to replace defective

lamps, and they also have back-up procedures for electronic records to mitigate the risk of losing data. Also, the reason why we qualify analytical equipment is to avoid unexpected bad performance leading to inaccurate results when using the equipment for sample analysis.

The industry frequently has problems to find a structured way of prioritizing risks. The FDA has frequently been asked to come up with a matrix of regulated processes indicating whether they are high or low risks. The FDA has made it very clear that this will not happen because each situation is different, but they did give criteria: impact on product quality and on patient safety.

General advice came from the FDA's John Murray when answering questions on the FDA's expectations at the IVT Computer System conference in May 2004 (66):

> *Really, I don't recommend you do a detailed risk assessment on every record in the building. I think you need to set up a systematic way of doing it – and you are going to put certain records in certain categories from the very beginning. If a record is used to release a product and this record is incorrect and you release an unsafe product – I would make that your highest category, direct impact to public health.*

Risk-based validation of laboratory systems consists of two steps:

1. Define the risk category, e.g., high, medium, or low.
2. For high and medium risk systems define the extent of validation for each category according to guidelines as defined by your company.

This chapter guides readers through a logical risk-based approach for laboratory systems. It gives recommendations on how to define the risks for different systems and validation tasks for risk categories during the entire life of the system. More details can be found in a risk management master plan authored by Huber (67). Portions of that document have been reprinted in this chapter.

It is quite obvious that there are no generally accepted models to copy, and there is no universal solution. Each company must figure out the answers for itself because success really depends on the specific situations for specific companies. The model suggested in this chapter is just one example for implementation. The FDA would allow many others. For example, this model suggests three risk categories: high, medium, and low. It would also be acceptable to have only two: high and low, or even five and more. All models would be accepted as long as the approach is justified and documented.

APPROACHES AND TOOLS FOR RISK ASSESSMENT AND MANAGEMENT

The types of risk a laboratory deals with include patient risk (safety and efficacy of drugs), regulatory risk (FDA 483s, warning letters, product recalls), financial risk through inability to get products approved for marketing, and risk due to inability to ship finished products or due to the consequences of unauthorized disclosure of trade secrets and private information. Risk management is the entire process from identifying and evaluating the risk to defining risk categories, and then taking steps to reduce the risk to an acceptable level. Risk assessment includes analysis and risk evaluation.

There are a number of standard risk assessment techniques available and widely used in the industry. The most important ones are the Failure Mode and Effects Analysis approach (FMEA), the Fault Tree Analysis (FTA) and the Hazard Analysis and Critical Control Point (HACCP) methodology. All three methods are described in brief by Mollah (68).

An approach widely used in the medical device industry is based on ISO Standard 14971 (69). While the FMEA and FTA are based more on quantitative statistical data, the ISO approach is more of a qualitative nature. The concept is to determine risk factors from their likelihood and severity, to mitigate risks, and to monitor and update the process if necessary. The model described by GAMP (61) is similar but adds detectability as another criterion; the more likely that the problem is being detected the lower the risk. Labcompliance has developed an extensive risk management master plan using the concept as described in the ISO Standard (67).

For the scope of this chapter we follow an approach as described in the ISO Standard (69). The used model is more qualitative than quantitative and very much based on the experience of users, validation groups, and auditors either with the same or with a similar system. Also, for the scope of the chapter we introduce readers to the concept of full risk management but then only focus on risk assessment. However, we should bear in mind that some of the current validation tasks such as vendor assessment and even testing are already steps towards risk mitigation of computer systems.

RISK MANAGEMENT OVERVIEW

Risk management of a laboratory system starts when the system is specified and purchased, it continues with installation and operation, and ends when the system is taken out of service and all critical data have been successfully migrated to a new system. The approach we take is to divide risk management into four phases, as illustrated in Figure 1.

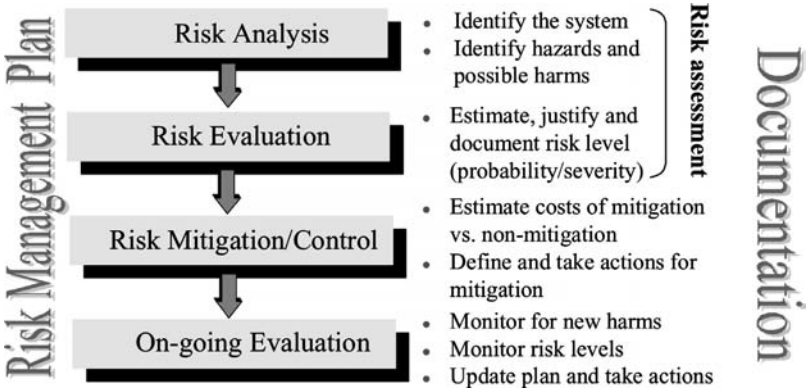


Figure 1 Risk management. *Source:* Ref. 67.

The phases include:

- **Risk Analysis** Define laboratory systems, components and software functions. Identify potential hazards and harms using inputs from system specifications, system administrators, system users, audit reports, infrastructure qualification, and system validation reports.
- **Risk Evaluation and Assessment** Define the severity and probability and risk of each hazard (e.g., by using past experience from the same or similar systems).
- **Risk Mitigation and Control** Determine acceptable levels of risk and identify the hazards that would need mitigation to reach those levels. Identify and implement steps to mitigate risks.
- **Ongoing (Re-)evaluation** Evaluate the system on an ongoing basis for new hazards and changes in risk levels. Adjust risk and mitigation strategy where necessary.

The most critical action during the risk assessment process is to define criteria for criticality, which finally determines the risk level. For example, the question frequently comes up: What if an inspector questions my decision? There is no absolute measure, so a dispute may arise. This discussion is similar to the discussion on computer validation 10 to 15 years ago when the question frequently came up regarding how much validation was enough. This question was nicely solved with the development of a validation master plan. Companies developed these kind of master plans on a fairly high level to guide validation specialists through the validation process by explaining the procedure for easy understanding, offering templates

for convenient implementation, and giving examples on what to validate for different systems.

An equivalent document in the area of risk assessment is a risk management master plan. Such a document should be developed at a fairly high level within a company or laboratory. It should describe the company's or laboratory's approach for risk management and assessment and should include templates for risk identification, evaluation, mitigation, and control. It should also include criteria and examples for severity and probability. The main advantages are increased efficiency and, even more important, consistent implementation. For more details on the contents see Reference 67. The master plan can be used to derive risk management plans for individual projects. The outcome of the risk assessment process should be documented in a risk management report.

RISK ANALYSIS

The first step in the risk management process is the risk analysis, sometimes also called risk identification or Preliminary Hazard Analysis (PHA). In this phase individual hazards are identified. The output of this phase is the input for risk evaluation.

Inputs for risk analysis are:

- Specifications of equipment/hardware/software
- User's experience with the same system already installed
- User's experience with similar systems
- Experience with the vendor of the system
- Failure rates of the same or a similar system (meantime between failures) and resulting system downtime
- Trends of failures
- System validation reports
- Out-of-specification results and failure investigations
- Internal and external audit results

Input can come from analysts, supervisors, the validation group, IT administrators for systems running on a network, or from QA personnel, e.g., as a result of findings from internal or external audits.

The project manager collects inputs on potential hazards with possible harms. For documentation purposes, forms should be used. The forms should have entry fields for the person who made the entry, risk description, possible hazards and harms, probability of occurrence, and possible methods of mitigation. An example is shown in Figure 2.

Name/Organization: Date:	System ID:	Location:	
Risk description	**Impact (possible harm)**	**Probability of occurrence**	**Method of mitigation**

Figure 2 Template to identify risks. *Source*: Ref. 67.

Occasional problems and harms with laboratory systems include, but are not limited to, the following:

- Inadequate vendor qualification and/or absent specifications on vendor support in the purchase agreement. This can result in reduced uptime because of missing support in the case of hardware, firmware, or software problems.
- Inadequate or absent installation documentation can make it difficult to diagnose a problem.
- Inadequate or absent verification of security access functions can result in unauthorized access to the system.
- An insufficient or absent plan for system backup can result in data loss in the case of a system failure.
- Inadequate change control procedures can cause problems after system changes.
- Poor or absent documentation of hardware and software changes makes it difficult to diagnose a problem.
- Inadequate corporate quality assurance policies and procedures or inadequate reviews to check if procedures are implemented and followed.

RISK EVALUATION PROCESS

This phase is used to categorize and prioritize the risk for business and compliance/health.

Data should be entered into a form with entry fields for risk descriptions, business (continuity) impact, product quality/safety, compliance impact, and probability of occurrence. An example is shown in Figure 3 and the various impacts are described below.

Name/Organization: Date:	Infrastructure ID:	Location:

Risk Description	Business Continuity Impact	Product Quality/ Safety	Compliance/ Integrity	Probability	Risk Factor

Business continuity impact	***Product quality/ safety***	***Compliance/ data integrity***	***Probability of occurrence***
High (3) *= >[a]$$$/day* *No replacement system* ***Medium (2)*** *= > $$$/day* *Replacement after one day* ***Low (1)*** *= > $$$/day*	***High (3)*** *Failure will probably cause an adverse effect on product quality/ consumer safety* ***Medium (2)*** *Failure is not likely to cause an adverse effect on product quality/consumer safety* ***Low (1)*** *Failure will not affect product quality/data integrity*	***High (3)*** *Loss or change of GxP critical data with product recall* ***Medium (2)*** *FDA warning letter* ***Low (1)*** *FDA 483 inspectional observation*	***High (3)*** ***Medium (2)*** ***Low (1)***

[a] $$$/day should be defined and added for individual projects as well as recommendations on how to quantify probability.

Figure 3 Template for risk evaluation. *Source*: Ref. 67.

- **Impact on Business Continuity** This is related to a company's ability to market a new product and reliance on the system uptime for continuous shipment of products. This answers the question: How big is the loss in due to delays in new product approval and shipment stoppages?

- **Impact on Product Quality** The question here is if the system has a direct impact on product quality, which means that any failure cannot be corrected before a new drug is approved for marketing or before a batch is released for shipment. An example for a high-risk system is an analysis system used in quality control where analysis results are used as criteria whether to release a batch or not.
- **Impact on People's Health and Safety** This section includes consumer safety and environmental hazards. An example for high severity is when poor product quality can cause death or when a system failure causes severe illness of operators. Because an impact on health and safety can only occur if there is also an impact on product quality, we combine both factors.
- **Impact on Compliance** This part is related to the risk of failing regulatory inspections and receiving single or multiple warning letters or inspectional observation reports. A typical compliance issue is inadequate integrity of regulated data.

There are other indirect factors such as claims by end-users, product recalls, and a company's reputation, e.g., if the health of a patient is affected.

Information from this categorization is used to calculate an overall risk factor. Risk categories are converted into numeric values; high $= 3$, medium $= 2$, low $= 1$. Risk factors are calculated using the following formula:

$$(\text{Business impact} + \text{Safety} + \text{Compliance impact}) \times \text{Occurrence} = \text{Risk Factor}$$

EXAMPLES FOR FACTORS CONTRIBUTING TO HIGH- AND LOW-RISK LEVELS

Factors contributing to high severity levels can be related to product quality and health and safety, the business community, and compliance:

Factors Related to Product Quality and Health/Safety

- Systems used in quality control laboratories for testing samples for product release
- Users interact manually with the system and data and can manipulate the data
- Failure of the system can have a direct impact on product quality
- No or low probability that the problem will be detected and can be corrected
- Product quality problems may lead to a person's death or serious and permanent injury

Factors Related to Business Continuity

- System must run 24 hours a day, 7 days a week
- Highly complex hardware, software and system configuration
- Highly customized
- Unskilled operators
- No workaround solutions
- Vendor not recognized in the pharmaceutical industry and/or no support from vendor, e.g., no documented evidence on validation during development, or no phone or on-site support in case of problems

Factors Related to Compliance

- Used for GMP-regulated applications
- Failure of the system can have an impact on data integrity or can cause loss of data

Factors contributing to low severity levels can be related to these categories as defined below:

Factors Related to Product Quality and Health/Safety

- System is used in early product development stage.
- System is fully automated and relies on well-validated processes.
- High probability that the problem will be detected and can be corrected.
- Product quality problems do not have any impact on a person's health.

Factors Related to Business Continuity

- Used occasionally.
- Highly skilled operators.
- Widely used commercial systems.
- No customization.
- Workaround solutions available.
- Full support from recognized vendor, e.g., documented evidence on validation during development, local language phone support, and/or on-site support in case of problems.

Factors Related to Compliance

- Not used in regulated applications.
- Failure of the system does not have any impact on data integrity and cannot cause loss of data.

PROBABILITY

Probability should answer the question, "What is the likelihood that the system fails, generates wrong data, or that data are lost?" Probability should be expressed in occurrence per time. We recommend using five categories:

- frequent (e.g., once every month),
- probable (e.g., once every one to three months),
- improbable (e.g., once every three to twelve months),
- occasional (e.g., once every one to three years), and
- impossible.

We use past experiences from the same or similar systems to estimate the probability. We use the same form as shown in Figure 3 and then add probability. From overall severity and probability we can then calculate the overall risk expressed by risk codes 3 (High), 2 (Medium), or 1 (Low).

EXAMPLES

Examples are quite useful to get an idea on what type of systems fall into different categories. The question frequently comes up if, for example, a laboratory management system or a documentation system falls into the high-, medium-, or low-risk category. Sometimes even systems from specific vendors are mentioned. These are the wrong questions. The risk is not dependent on the system functionality but rather on the records created, evaluated, transmitted, or archived by the system. A LIMS in a nonregulated research department is never a high-compliance risk system. On the other hand, a Laboratory Information Management System (LIMS) in a pharmaceutical quality control laboratory is most likely a high-risk system.

The primary questions should always be:

1. What is the impact if the system does not generate data or if the data are wrong?

2. For systems with high impact: Which subsystems or functions will most likely cause a failure or problem?
3. What can we do to reduce the risk that something goes wrong?

With the structured approach as explained in the previous sections it should be possible to answer these questions for each process or system. As explained above, the only way is to look at the records generated or handled by the system. Also, the same record type may belong to different risk categories. Let's take the example of an SOP: If it is used to instruct an analyst on how to analyze a sample for product release, it is a medium- or even high-risk record. On the other hand, if an SOP is used to qualify an environmental monitoring system, it would be a low-risk record.

GAMP has developed a good practices guide called Risk-Based Approaches to Compliant Electronic Records and Signatures (70). The guide has tables which list typical impacts by record type. Impacts are classified into high, medium, and low. Most records can belong to two categories, depending on the use of the record. For example, monitoring records can have a high, medium, or low impact depending on the criticality of the parameters being monitored.

Examples for high-impact laboratory records are:

- QC analysis test results if used for final product release decisions
- Investigations relevant to product release
- Bioequivalency study reports

Examples for medium- to high-impact laboratory records are:

- Equipment cleaning records
- Calibration/validation records
- Equipment maintenance records
- Finished (drug) product specifications

Examples for low- to medium-impact laboratory records are:

- SOPs
- Calibration/validation records
- Equipment maintenance records
- Finished (drug) product specifications
- Review and approval records
- Training records

An example for low-impact laboratory records is:

- Planning documents

Once the risk level of a record has been defined, the risk of the system generating or handling the records can also be estimated. High-risk systems typically have a direct impact on product quality or patient safety. Examples are systems used in pharmaceutical manufacturing and quality control such as electronic batch record systems, analytical control systems, and also document management systems and databases with high-risk records.

Medium impact systems typically have an indirect impact on product quality or patient safety. They are used to support systems classified as high-risk or to demonstrate evidence of compliance of records generated by the systems. Examples would be systems that are used to calibrate, qualify, and monitor the systems defined as high-risk. These would also include configuration management systems, calibration scheduling, and training record systems.

Examples of low-risk systems are word-processing systems that are used, for example, to generate validation plans or validation records. One of the reasons for low-risk systems is that the likelihood that they have errors is relatively low, errors would most likely be detected by proofreading, and such errors would most likely not have a direct impact on product quality and patient safety.

RISK-BASED VALIDATION TASKS AND OTHER CONTROLS

Once the risk level of a system is identified, validation tasks and other controls for systems can be defined. The risk level information is used for considerations such as:

- How detailed do we specify the system? For example, for low-risk systems we only prepare a high-level system description and for high-risk systems we develop detailed system requirement specifications.
- How extensively do we test the laboratory system? For example, high-risk systems are tested under normal and high-load conditions. Test cases are linked to the requirement specifications.
- How much equipment redundancy do we need? For example, for high-risk systems, we should have validated redundant hardware for

all components. For medium-risk systems, redundancy of the most critical components is enough, and for low-risk systems, there is no need for redundancy.

- How frequently do we have to back up data generated by the system? While a daily backup is a must for high-risk systems, a weekly incremental backup is sufficient for low-risk systems.
- What type of vendor assessment is required? For example, high-risk systems will require vendor audits while for medium- and low-risk an audit checklist and documented experience from the vendor should be enough.
- Which Part 11 requirements should be implemented in computerized systems? For example, for high-risk systems, computer-generated audit trails should be implemented, while for low-risk systems, a paper-based manual audit trail is enough.
- How to handle change control? While QA should approve all changes to a high risk system, for lowrisk systems it is enough to record changes by the user.
- How to handle system access? High-risk systems, e.g., database servers in a data center, should only be accessible through physical key locks or pass cards. Personal computer (PC) clients are accessible through entering user ID and passwords.

Validation tasks should be defined for each phase, starting with planning through to specification settings, vendor qualification, installation, testing, and ongoing system control.

The tasks should be consistent within an organization for each risk category. They should be well documented and included either in the risk management master plan or in the validation master plan.

Table 1 summarizes examples with validation activities for each validation phase and task. Table 2 shows a list of system controls with actions associated with them for each risk category.

Tables 1 and 2 are recommended as a starting point for a commercial off-the-shelf system with minor or no customization. The extent of validation increases for systems with major customization or for software that is developed by or for a specific user. For example, in this case each user-specific function should be fully tested.

Table 1 Examples for Risk-Based Validation Tasks.

Validation Phase	High	Medium	Low
Planning	Detailed validation plan with all activities, deliverables, owners and timetables.	High-level plan with key activities.	No specific project validation plan. Follow template for low-risk applications.
Specifications	Document all requirements. Uniquely number all requirements. Define critical vs. non-critical requirements.	Document all requirements. Uniquely number all requirements.	No specifications. Refer to vendor documentation.
Vendor assessment	Direct vendor audit or 3rd party audit.	Review of vendor documentation. Mail audit.	Document vendor.
Installation	Document system and all components and configurations. Verify correct hardware and software installation. Document software versions.	Document system and all components and configurations. Document software versions.	Document equipment hardware, software and version.
Functional testing	Test all critical standard functions. Test over entire applications range. Include high-load and stress tests. Test correct functioning of user specific configurations. Link tests to requirements.	Test all critical standard functions under high and normal load. Test correct functioning of user specific configurations.	No testing.
On-going control	Regular virus check. Regular revalidation. Regular regression testing.	Regular virus check. Regular regression testing.	Regular virus check.

Source: Ref. 67.

Table 2 Examples for Risk-Based System Controls

Access control	Through key lock or pass cards and user ID/password	Through user ID/password	Through user ID/password
All changes approved by system owner and QA	All changes approved by system owner	All changes documented by user	
Computer system audits	Regular audit of system and sub-systems Regular review of the audit plan	"For cause" audits in case of problems	No audits
Contingency planning	Redundancy for all hardware	Redundancy for key hardware, e.g., server	No redundancy
Backup	Daily incremental backup Weekly complete backup	Daily incremental backup	Weekly incremental backup
Record retention and archiving	Formal retention procedure On-site and off-site storage	Formal retention procedure On-site storage	On-site storage

Source: Ref. 67.

Summary Recommendations

1. Develop a risk-management master plan as a framework for individual risk-management activities.
2. Define criteria for risk levels of records with probability and severity.
3. Define criteria for validation steps.
4. For each project develop a risk-management project plan.
5. Justify and document the outcome of the risk-assessment process in a risk-assessment report.

5

Master and Project Planning for Equipment and Computer Systems

What Is Discussed in this Chapter?

1. The importance of master plans
2. Corporate versus site and department master plans
3. Contents of master plans
4. The relationship between master plans and project plans
5. Contents of project plans

THE IMPORTANCE OF MASTER PLANS

Master plans are documents that lay out a company's approach for specific activities, e.g., how to achieve compliance for a laboratory. The equipment qualification master plan describes the company's approach for qualifying equipment such as analytical instruments. It also details steps for equipment qualification and owners and deliverables for the qualification phases.

All qualification and validation activities should be described in a master plan, which should provide a framework for thorough and consistent validation and qualification. A validation master plan is officially required by Annex 15 to the European GMP Directive (17): "All validation activities should be planned. The key elements of a validation programme should be clearly defined and documented in a Validation Master Plan (VMP) or equivalent documents." The PIC/S guidance Good Practises for Computerised Systems in Regulated GxP Environments (21) states in section 7.3: "It would be expected that the regulated user's Validation Policy or Validation Master Plan (VMP) should identify the company's approach to validation and its overall philosophy with regards to computerised systems . . . "

FDA regulations and guidelines don't mandate a validation master plan. However, inspectors want to know the company's approach towards validation. The validation master plan is an ideal tool to communicate this approach both internally and to inspectors. It also ensures consistent implementation of validation practices and makes validation activities much more efficient. If there are any questions as to why things have been done or not done, the validation master plan should give the answer.

A master plan has four objectives:

1. It serves as a resource for development of equipment qualification and system validation project plans. This will help make planning more consistent and efficient.
2. It answers the inspector's question on the company's approach for validation. A validation master plan is officially required by the European GMP Directive through Annex 15.
3. It demonstrates corporate commitment and support for equipment qualification and computer system validation through the corporate policy statement.
4. It helps personnel at all management levels understand how qualification and validation is approached and implemented in the organization. So, it is a good training tool.

Within an organization a validation master plan can be developed for:

- corporate
- single sites or locations
- single system categories
- department categories, e.g., for all departments within a company

Depending on the size and organization of a company, there can also be several levels of master plans, for example, at a corporate level, at a site level, and at a department level. If there are several such plans, they should be linked. Project plans are developed for individual projects using the master plan as frame work. The relationship between different master plans and the project plan is shown in Figure 1.

The corporate master plan is the highest level framework. The plan should be developed by a cross-functional task force with members from all groups that will be impacted by the plan. The plan should be flexible enough so that it can be used for master plans at different locations without too much customization. It should include a company policy and approaches for validation. It should also include forms, templates, and examples to ensure efficient and consistent implementation of site master plans and plans for individual validation/qualification projects. If there is no specific need to change

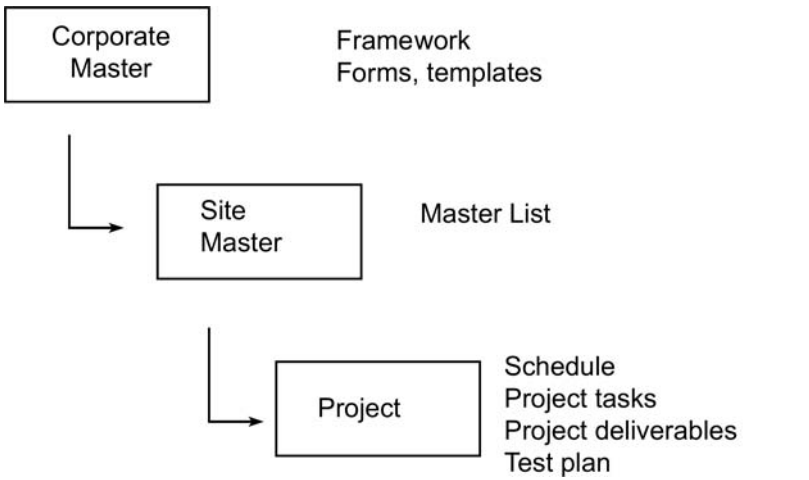


Figure 1 Relationship between master plans and project plans.

approaches described for specific sites, the corporate plan can be used, complemented with a list of equipment existing at the site. Contents for such a list should include information on if the equipment is used for GxP environments and also information on the risk level of a system. For systems not validated or qualified, a time frame should be given on when the equipment will be validated. A template with an example is shown in Table 1. A project validation plan should be developed from the site master plan for individual projects.

CONTENTS OF MASTER PLANS

It is important that master plans include the right level of information. There is often a question about how many pages a master plan should have.

Table 1 Template and Example for Equipment Master List

ID	Description	Location	Application	GxP	Risk	System Owner Contact	Time Frame for Validation
RV3212	HPLC Analysis System	Lab 4 West 1	QC Analysis	Yes	High	Bill Hinch TN 432 23	Jan-April 2008

There is no definite answer but five pages would not be enough and 50 pages are too much. Twenty to thirty pages should be sufficient to accommodate all information that should include items as listed and described in Table 2.

Table 2 Contents of Validation Master Plan

Topic	Contents
Introduction	Scope and objective of the plan. Example: What equipment and locations are covered by the plan.
Responsibilities	Responsibilities by function and qualification requirements. Validation committees, system owners, project teams, IT/IS, quality assurance, user departments, documentation department, suppliers, and plant maintenance.
Related documents	This lists documents related to the master plan. This could be other master plans such as a risk management master plan, a security plan, or a network plan. It could also be procedures or references to external procedures.
Products/processes to be validated and/or qualified	This section has two parts: 1) Part one gives general recommendations: what type of equipment should be validated. 2) Part two refers to an appendix with an equipment master list.
Qualification/Validation approach	This part describes the company's approaches for equipment qualification and system validation. Examples are the V model or 4Q life-cycle phases validation.
Risk management	Describes the risk management approach and includes examples of risk categories and recommended qualification and validation tasks for different risk categories.
Vendor management	Describes how vendors are selected and assessed for different equipment categories.
Steps for qualification and validation	This section includes detailed steps for validation phases such as DQ, IQ, OQ, and PQ. It also includes recommendations for a test plan, for type and extent of testing, and for the test environment. In addition it describes what should be included in a validation report.

(*Continued*)

Table 2 Contents of Validation Master Plan (*Continued*)

Topic	Contents
Handling existing equipment	This section describes the approaches for equipment already existing in the laboratory but not yet validated.
Change control	This section is very important for all equipment and systems. It should give detailed information on changes. It describes who can initiate, authorize, implement, and release changes and how changes should be documented.
Backup and recovery	This section is only important for equipment that can store electronic records. It should describe the philosophy for backup and how to validate backup and recovery procedures.
Maintenance and support	This section should include recommendations for regular preventive maintenance and security.
Contingency planning and disaster recovery	This part describes what to do in case equipment fails. Example: Which equipment needs redundancy or UPS?
Requalification criteria	Recommendations when equipment needs to be requalified and what should be tested during requalification.
System retirement	Describes actions when systems are taken out of service.
Training	Describes how operators are trained and how trainings are documented.
Validation procedures	This should list all procedures that are necessary to complete the validation project.
List of procedures and deliverables	Lists documentation that should be generated during the validation.
Deviations	Describes how deviations from a validation plan should be handled.
Glossary	Includes acronyms and description of terms.
Attachments	• Equipment master list. • Members of the validation committees. • Templates for project schedule.

CONTENTS OF PROJECT PLANS

The qualification of individual equipment should be carefully planned and should be described in a project plan. The contents items are similar to the master plan but the project plan is more specific. For example, responsibilities are defined by a person's name and not by functions, and the project schedule includes exact dates and not only time frames.

For simple equipment without computer systems such as a pH-meter or a photometer, templates in table form are sufficient. Plan items are entered into the cells. For larger projects a detailed individual validation project plan should be developed. An example would be implementing a LIMS or a networked chromatographic data system. This plan is also derived from the validation master plan using the principles and templates from the master plan. It formalizes qualification and validation and outlines what is to be done in order to bring a specific system into compliance. For inspectors it is a first indication on which control a department has over a specific system and it also gives a first impression of the validation quality. For the management it should provide information on required resources and timelines so that the validation costs can be estimated.

The plan should be developed by a cross-functional team. Members should represent all groups that may use the plan. The plan should preferably be developed through team meetings. Depending on the complexity of the project these meetings can take from one or several days up to two to three weeks.

A validation project plan should include the following sections:

- Introduction
- Scope of the system, what it includes and what it doesn't include.
- System description, its intended use and intended location.
- Anticipated users of the system.
- Validation approach, for example, life-cycle model.
- Assumptions, limitations, and exclusions.
- Responsibilities: Who is expected to do what.
- Risk assessment: Risk level and justification.
- Risk-based test strategy and approach for validation steps, e.g., DQ, IQ, OQ, and ongoing performance control.
- Change control and revalidation.
- Handling system security.
- Data backup and recovery.
- Contingency planning.
- Deviation handling.
- List with required procedures.

- List with expected validation protocols and other deliverables.
- Timeline, owners, and deliverables for each phase.
- Glossary
- Section with final approval or rejection statement and signatures.

Summary Recommendations

1. Develop a high-level validation master plan for equipment and computer systems, either on a corporate or site level.
2. Include validation approaches, examples, and templates.
3. The master plan should be developed by a cross-functional team that represents all anticipated users of the plan.
4. For each project develop project plans.
5. Use the master plan as a framework to derive the project plan.
6. For large companies three plan levels are recommended; corporate, site, and project.

6

Design Qualification

What Is Discussed in this Chapter?

1. Definition of design qualification (DQ)
2. Importance of DQ
3. Steps for DQ
4. How vendors can help with DQ
5. Steps for vendor qualification

DEFINITION

Bedson and Sargent offer the following definition of design qualification:

> *Design qualification defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier (30).*

DQ should ensure that instruments have all the necessary functions and performance that will enable them to be successfully implemented for the intended application and to meet business requirements. The DQ phase should also verify that the equipment has been developed in a quality control environment and that the vendor can support the equipment during installation and ongoing use.

Errors in DQ can have a tremendous technical, compliance, 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 a poor quality system or with insufficient support capability can decrease instrument uptime with a negative business impact.

While IQ, OQ, and PQ are being performed in most regulated laboratories, DQ is not so well known to many laboratories. It is rarely performed officially in those cases where the equipment is planned for use in multiple applications, not in a specific one. When the author has presented the concept of equipment qualification in seminars, attendees always agreed that the concepts of IQ, OQ, and PQ are essential for analytical laboratories, but many have not been convinced that this also holds true for DQ. The situation becomes clearer when we look the key user activities during the DQ phase, which are (1) writing user requirements, and (2) assessment of the supplier.

These activities are performed in most laboratories but are not called DQ, so is this a problem? DQ is officially required by Annex 15 of the EU Guide for Good Manufacturing Practices (17):

> *The first element of the validation of new facilities, systems or equipment could be design qualification (DQ).*

Therefore inspectors from Europe and from other PIC/S member countries are quite familiar with the term and may ask for DQ documents. An FDA inspector may ask for documented user requirements and for more complex systems also for documented vendor assessment.

The main purpose of DQ is to ensure that

- the right type of equipment is selected for specific tasks,
- the equipment will have the right functional and performance specifications, and
- the vendor meets the user firm's qualification and support criteria.

DQ should be performed

- when a new instrument is being purchased, or
- when an existing instrument is being used for a new application not previously specified.

RECOMMENDED STEPS IN DESIGN QUALIFICATION

Table 1 lists recommended steps that should be considered for inclusion in a design qualification.

USER REQUIREMENTS SPECIFICATIONS

User requirement specifications (URS) define what the user wants to do with the equipment and should be written by typical equipment users. URS are

Table 1 Steps in Design Qualification

- Describe the intended use of the analysis
- Select the analysis technique
- Describe the intended use of the equipment
- Describe the intended environment
- Define user requirement specifications (URS)
- Preliminarily select the functional and performance specifications (technical, environmental, safety)
- Preliminarily select the supplier
- Test the selected instrument (only recommended if the technique is new)
- Finally, select the equipment and supplier
- Document the rational behind the selection of the system and supplier
- Document the final functional and operational specifications

an important foundation of equipment qualification and computer validation. For equipment hardware, URS should include a list of all functions the equipment should perform; it also should list performance specifications and should specify any physical hardware characteristics, such as maximum size or access to maintenance parts from the front of an instrument. For software, URS should list all functions required by the application. They also should include functions required by regulations, such as limited authorized access to the system and data and electronic audit trail.

Writing user requirement specifications for analytical equipment hardware is relatively easy. Users are familiar with the type of instrumentation, the number of specifications is relatively small, and users typically know exactly what they need. Also, equipment functions and also performance is well specified and specifications are readily available from suppliers. For convenience, the vendor's specification sheets can be used as guidelines. Simply declaring the vendor's specifications as the official URS document is not recommended because compliance to the functional and performance specifications must be verified later in the process, during OQ and PQ. Specifying too many functions and setting the values too stringently will significantly increase the workload for OQ.

It is frequently the case that instruments are used for different applications with different functional and performance 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.

Table 2 includes an example for requirement specifications. The parameters can be easily adapted to other applications. The table can be used as a basis to write any design qualification.

VENDOR QUALIFICATION

As part of the DQ process, the vendor should be qualified. The question is, how should this be done? Is an established and documented quality system enough (e.g., ISO 9000)? Should there be a direct audit? Is there another alternative between these two extremes?

For equipment hardware, adherence to a well-established quality system is enough evidence for the vendor's ability and practices to design, develop, manufacture, and support equipment in a quality environment.

In most cases, it is also a question of confidence between the vendor and the user's firm. Unfortunately, confidence is not taken into account in

Table 2 Selected Examples for Requirement Specifications[a]

Design Qualification	Selected Examples
Intended environment and use	The system will be used in a quality control laboratory to analyze impurities. The laboratory is regulated by U.S. FDA and European GMPs.
User requirement specification for the HPLC analysis	1. 20 samples/day 2. Automated unattended sample injection, HPLC analysis, data evaluation, and printing 3. Limit of quantitation: <0.03 %
Functional specifications	
Pump	1. Binary or higher gradient 2. Flow rate: 0.5 to 5 ml/min 3. Must have on-line vacuum degasser 4. Flow cell must be accessible from the front
Detector	1. UV/Vis Variable wavelength detector 2. Wavelength range: 200 to 600 nm 3. Flow cell and lamp must be accessible from the front for easy maintenance
Autosampler	1. Must accommodate at least 100 samples with 2 ml volume or at least 25 samples with 5 ml volume 2. Variable sample volume from 1 μl to 5 ml without hardware change 3. Needle flush and wash to minimize sample carry over
Column compartment	1. Operating range 20 to 40 Deg C, peltier controlled 2. Must accommodate at least 2 columns with length of up to 25 cm

(*Continued*)

Table 2 Selected Examples for Requirement Specifications (*Continued*)

Design Qualification	Selected Examples
System	1. Ability to detect leaks in each module and to switch the pump in case a leak is detected 2. Maintenance parts accessible from the front
Computer and software	1. Microsoft XP or VISTA operating system 2. Control of all module and system parameters 3. Data acquisition, peak integration, and quantitation 4. Automated method sequencing for unattended injection of different samples 5. Electronically save and retrieve all chromatograms and method parameters generated and used by the system 6. Database for storage of and search for data 7. Limited and authorized access to the system, applications, and data 8. Recording of unusual events in an electronic log-book 9. Software for routine diagnostics and troubleshooting hints

[a] Incomplete.

arguments with the FDA. So how should one proceed? The exact procedure depends very much on the individual situation. For example, if the equipment does not include a computer system, certification to ISO 9001 or an equivalent system is sufficient. On the other hand, for a complex LIMS a more detailed assessment is necessary.

Table 3 describes steps recommended for supplier qualification. Table 4 includes an example for vendor assessment documentation. For equipment with computer systems it is more complex. Detailed recommendations and examples for assessment of software and computer system supplies can be found in Reference 61.

Table 3 Steps for Vendor Qualification

1. Develop a vendor qualification checklist. This list should include questions on how the equipment is developed, validated, installed, and supported. The most important questions are: • Does the vendor have a documented and certified quality system (e.g., ISO 9001)?

(*Continued*)

Table 3 Steps for Vendor Qualification (*Continued*)

- Is equipment hardware developed and manufactured according to a documented procedure?
- Are tests documented and traceable to design and requirement 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 enhancement request?
- Is there a change control system with appropriate notification of users subsequent to changes?
- Will the vendor allow an audit if such a need comes up?

2. Send the checklist to the vendor. If the vendor answers all the questions satisfactorily within a given time frame, 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.

Table 4 Supplier Qualification for Equipment Hardware

	Requirement	Supplier offering	Requirement met
Quality system	Supplier must provide documented evidence that the product has been designed, developed and manufactured in a quality environment	Supplier has ISO 9001:2000 certification	Yes
Training	Supplier must provide operator training	Supplier provides onsite operator training	Yes
Installation qualification	Supplier must provide installation and installation qualification services	Supplier installs the product and performs installation qualification	Yes
Operational qualification	Supplier must provide operational qualification services	Supplier provides operational qualification services	Yes

(*Continued*)

Table 4 Supplier Qualification for Equipment Hardware (*Continued*)

	Requirement	Supplier offering	Requirement met
Product support	Supplier must provide phone and on-site support in case of defects	Supplier provides phone and on-site support in case of defects and other problems	Yes
Upgrade support	Supplier must provide information through the internet on availability of new firmware upgrades	Supplier has a user accessible website with information on availability of new firmware upgrades	Yes

Summary Recommendations

1. Develop a procedure for DQ.
2. Develop a procedure for requirement specifications.
3. Develop a procedure for vendor qualification.
4. Define the intended use of the equipment.
5. Define the required functions of the equipment (use the vendor‘s instrument specifications list for help).
6. Qualify the vendor, based on references (internal and external) and/or by using mail audit checklists.

7

Installation Qualification

What Is Discussed in this Chapter?

1. Definition of installation qualification (IQ)
2. Steps for IQ
3. The line between IQ and OQ
4. Documentation that should be generated
5. Performance of IQ—the vendor or the user

DEFINITION

Bedson and Sargent's definition of installation qualification is as follows:

> *Installation qualification establishes that the instrument is delivered 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 (30).*

The main purposes of IQ are to ensure that the

- equipment has been received as purchased,
- the equipment meets the physical hardware specification,
- the selected environment meets the vendor's environmental specifications,
- individual hardware modules and all accessories are properly installed and connected to each other,
- the software is completely installed on the designated storage device,
- computer systems are properly configured for the intended use,
- the instrument functions in the selected environment, and
- all equipment hardware and software are registered in some kind of a laboratory equipment database.

This chapter discusses issues that involve preparation for installation: installation of hardware and software, functional testing of modules and systems, and preparing the documentation. IQ should follow a process that can be documented as a (standard) operating procedure.

PRE-INSTALLATION

Before the instrument arrives at the user's laboratory, serious thought must be given to its location and space requirements. A comprehensive understanding of the requirements for the new equipment must be obtained from the vendor well in advance: required bench or floor space, environmental conditions such as humidity and temperature, and, in certain cases, the utility needs such as electricity or compressed gases for gas chromatographs. Care should be taken that all of the environmental conditions and electrical grounding are within the limits specified by the vendor and that the correct cables are used. If environmental conditions might influence the validity of test results, the laboratory should have facilities to monitor and record these conditions when using the equipment, either continuously or at regular intervals. Examples are measurements of environmental temperature and humidity if the instruments are operated close to the specified limits.

Any special safety precautions should be considered (for example, for radioactivity measurement devices), and the location should also be checked for any devices generating electromagnetic fields in close proximity. Table 1 lists the recommended steps before installation.

INSTALLATION

When the instrument arrives, the shipment should be checked for completeness by the user. It should be confirmed that the equipment ordered is what was in fact received. In addition to the equipment hardware, other items should be checked, e.g., cables, other accessories, and documentation. A visual

Table 1 Steps 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, vibration level, and dust).
- Allow sufficient shelf space for the equipment, SOPs, operating manuals, and software.

Table 2 Steps During Installation

1. Compare equipment, as received, with purchase order, including:
   - software,
   - accessories,
   - spare parts, and
   - consumables.
2. Check documentation for completeness:
   - operating manuals
   - maintenance instructions
   - standard operating procedures for testing and safety
   - validation certificates
   - health and safety instructions
3. Check equipment for any damage.
4. Read the supplier's instruction for installation.
5. Read the supplier's safety instructions, if there are any.
6. Install hardware (computer, equipment, fittings and tubings for fluid connections, columns in HPLC and GC, power cables, data flow and instrument control cables) following the manufacturer's recommendation.
7. Switch on the instruments and ensure that all modules power up and perform an electronic self-test. Check if the instrument does what is described in the supplier's documents. Record any deviations.
8. Install software on computer following the manufacturer's recommendation.
8. Verify correct software installation, e.g., are all files loaded. Utilities to do this should be included in the software itself.
10. Make backup copy of software.
12. Configure peripherals, e.g., printers and equipment modules.
13. Identify and make a list with a description of all hardware, include drawings where appropriate.
14. Make a list with a description of all software installed on the computer.
15. Develop drawings for complex systems, for example, for client/server data systems.
15. List equipment manuals and SOPs.
16. Prepare an installation report.

inspection of the entire hardware system should follow to identify any physical damage. For more complex instrumentation, for example, if a single computer controls and/or acquires data from several analytical instruments, wiring diagrams should be produced if they were not supplied by the vendor. An electrical test of all modules and systems should follow. The impact of electrical devices close to the computer system should be considered and evaluated if the need arises. For example, when variable voltages are sent between sensors and integrators or computers, electromagnetic energy emitted by poorly shielded fluorescent lamps in close proximity or by motors can

Table 3 Equipment Hardware Characterization

- Internal identification number (asset number)
- Description of the piece of equipment
- The manufacturer's name, address and phone number for service calls, service contract number, if there is one
- Serial number of the equipment
- Firmware revision number of equipment
- Date received
- Date placed in service
- Current location
- Size, weight
- Condition when received, for example, new, used, reconditioned
- List with authorized users and responsible person(s)

interfere with the transmitted data. Table 2 lists steps as recommended during installation.

When the installation procedure is completed, both hardware and software should be well documented with model, serial, and revision numbers.

For larger laboratories with large amounts of equipment, a computer database for the storage of instrument records is preferable. Items that should be included for each piece of equipment are listed in Table 3.

Detailed documentation is even more important for computer systems than for equipment hardware. Documentation should include items such as the size of the hard disk, internal memory (RAM), installed type and version of operating software, standard application software, and user-contributed software, e.g., MACRO programs; (Table 4). This information is important because each item can influence the overall performance of a computer system. The information should be readily available when a problem occurs with the computer system.

TESTS DURING INSTALLATION

One question that frequently arises is whether any type of testing should be done as part of IQ. Frequent questions include: "Should there be any test?" and "Should testing include functional, operational, and performance measurements?"

Operational and performance testing do not belong in IQ; they belong in OQ. IQ should include tests only 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

Table 4 Examples for Computer System Identification

Computer Hardware	**Connected Equipment Hardware**
Manufacturer, model	Hardware module 1
Serial number	Interface card setting
Processor	
Internal memory (RAM)	**Operating software**
Graphics adapter	Operating system (version)
Hard disk (partitions, memory sizes)	User interface (version)
LAN interface	
Space requirement	**Application software 1**
	Description
Monitor	Manufacturer/vendor
Manufacturer, Model	Product number (version)
Serial number	Required disk space
Printer	**Application software 2**
Manufacturer, model	Description
Serial number	Manufacturer/vendor
Space requirement	Product number (version)
	Required disk space
Instrument interface card	
Type, select code, slot number	

any error messages during boot-up. 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.

Hardware Modules

Modern equipment hardware modules typically include a self-test program. They are performed every time the instrument is switched on; Table 5 lists typical electronic self-tests during instrument startup. The display of the message "self-test passed" is enough proof for successful installation (Fig. 1).

Computer Systems

When complex software is installed on a computer, the correctness and completeness of the installed program and data files should be verified. Vendors can assist in this process by supplying installation reference files and automated validated verification procedures. In this case, the integrity of each file is verified by comparing the cross-redundancy check (CRC) of the installed

Table 5 Typical Electronic Self-tests during Instrument Start-up

- Read-Only Memory (ROM) test
  This test is performed automatically every time the instrument is started. It checks the integrity of the ROM processor by comparing the actual checksum number with the original checksum number burned into the ROM.
- Random Access Memory (RAM) test
  Run during instrument start-up, a series of numbers are written to and read from the processor RAM memory. Both series of numbers must be identical to pass this test.
- Display test
  To ensure that all important user information is visible, the operation of all display devices including LEDs and status and error lamps are checked.
- Remote connections
  This tests the communications to and from external devices and checks their status: ready, not-ready, error. This is an important function that enables any module to shut down the pumping device should a leak be detected anywhere in the system.

file with the checksum of the original file recorded on the installation master. Modified or corrupt files have different checksums and are thus detected by the verification program. Verification reports should include a list of missing, changed, and identical files (Fig. 2).

Computerized Analytical Systems

Two critical installation items for a multi-module computerized system are the correct installation of fluid and electrical connections between different modules and the electrical connections between the computer hardware and the equipment hardware. This can be checked most efficiently by running

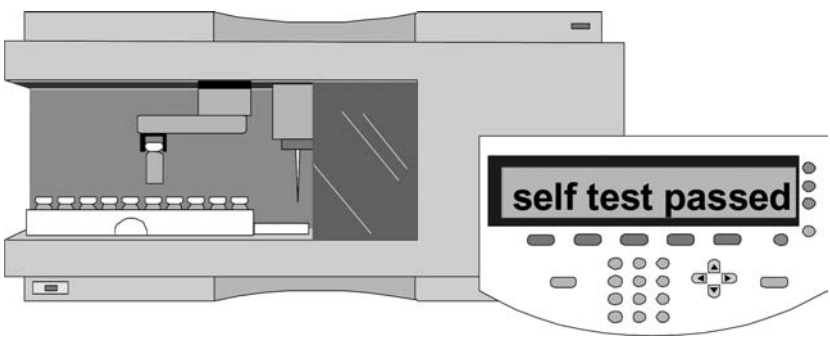


Figure 1 Equipment modules have a built-in electronic self-test program for instrument startup.

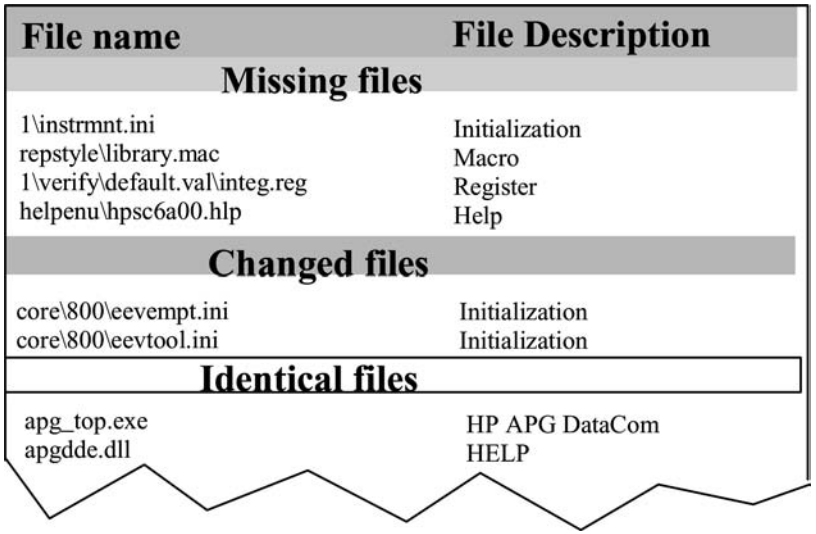


Figure 2 Installation verification report.

a well-characterized sample through the system to acquire and evaluate the data using standardized methods and compare the computer printout (spectra or chromatograms) with reference plots. When the actual plots agree with the reference plots, this is enough evidence of a successful system installation (Fig. 3).

THE INSTALLATION QUALIFICATION PROTOCOL

The installation should end with the generation and sign-off of the installation report referred to as the IQ document. The document should be signed by the user's representative, if the IQ was done by the user, and by the vendor's and the user's representative, if the IQ was done by the vendor.

It is recommended that documented procedures with pre-printed forms for the installation report be used. It is also recommended to make copies of all important documentation; one copy should be placed close to the instrument, and the other kept in a safe place. An identification sticker should be put on the instrument with information to include the instrument's serial number and the company's asset number.

The IQ protocol should include the following:

- Scope of the IQ protocol
- Protocol acceptance/approval by the user

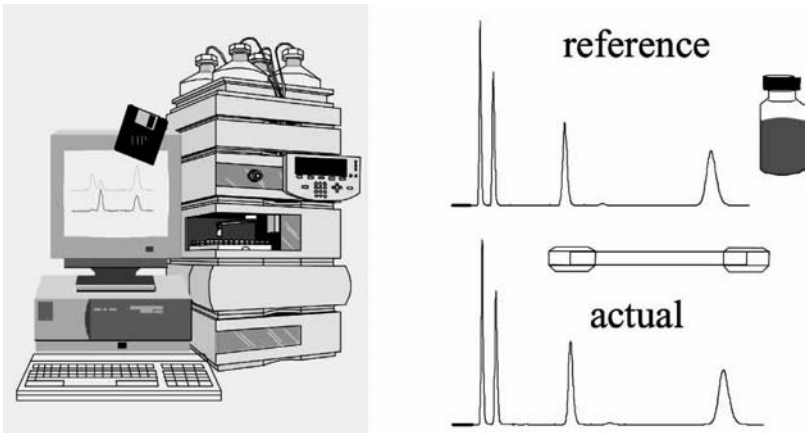


Figure 3 A system installation can be verified by analyzing a reference sample under well-characterized conditions and by comparing the actual plot with a reference plot.

- Protocol acceptance/approval by the vendor (if installation was performed by the vendor)
- Document revision history
- Listing of all instrumentation, including manufacturer, model and serial number, and so on
- List of user manuals and other documentation
- Procedure and results of module and/or system installation checks

Appendices should be attached that include the following:

- Purchase order
- Manufacturer's recommendation regarding the installation (they should include environmental limits, e.g., temperature and humidity), power, and gas supply requirements
- Reference plots and printouts of results from installation testing
- Wiring diagram (for complex systems)
- Software status bulletin describing any known defects of the system and giving temporary workaround solutions

REQUALIFICATION AFTER CHANGES TO THE SYSTEM

Any changes to the system should be thoroughly recorded and documented in order to maintain the qualification process. These may be replacements of modules or hardware, firmware, or software upgrades. Depending on the change, the tests as described in the previous sections should be repeated, and the results should be documented.

Summary Recommendations

1. Develop an operating procedure for IQ.
2. Generate a database for equipment.
3. Ask the vendor to perform IQ as part of the installation.
4. Correct installation of software should be verified for computer systems. Develop an installation verification master file.
5. An installation check with known chemical standards should be performed for complex modular systems.
6. Document IQ. If IQ was done by the vendor, the IQ document should also be signed by the vendor and user.

8

Operational Qualification

What Is Discussed in this Chapter?

1. The steps required for operational qualification (OQ)
2. Selecting tests and acceptance criteria for OQ
3. How to document OQ
4. The criteria for requalification

DEFINITION

Operational qualification is the process of demonstrating that an instrument will function according to its operational specification in the selected environment (30).

The main purpose of OQ is to ensure that (a) the equipment's hardware meets functional and performance specifications as required for the intended application and as specified in the DQ document, and (b) the computer software meets functional specifications as required for the intended application and as specified in the DQ document.

OQ should be carried out after initial installation; after instrument repair and after other major events, such as upgrades; and at regular intervals during routine use.

OQ is an important part of the overall equipment qualification process. The careful selection of test items, the test procedures, and acceptance limits is

extremely important, because if set too stringently, the instrument's test may have an unnecessarily high failure rate and/or the maintenance efforts will be too intense. If the limits are too relaxed, the equipment will not prove itself fit for its purpose.

The general procedure to qualify an instrument for operation is as follows:

1. Define the intended use and the functional and operational specifications (use criteria as defined during DQ).
2. Develop test procedures and protocols.
3. Define acceptance criteria.
4. Perform the tests.
5. Check if test results meet acceptance criteria
6. Document the results.
7. Develop criteria and steps for requalification, e.g., after repair.
8. Develop procedures in case the equipment does not perform to specifications.

While most analytical scientists today agree on the definition of OQ, agree on the general procedure for performing OQ, and have some idea about the test procedure, they are still unsure about implementation. Questions also arise regarding requalification after instrument upgrade and repair or when the instrument is moved to another lab. Frequent questions regarding OQ are as follows:

1. What procedures and test standards should be used? Should they reflect the intended use of the equipment, or should they be generic for the instrument category?
2. What should the acceptance criteria be? Should they be in line with the manufacturer's specifications, or should they reflect the intended use of the equipment?
3. Should the same procedures and acceptance criteria be used for all instruments of the same type in my laboratory and/or in our company?
4. For modular systems, should each module be tested, or is it enough to test the system as a whole?
5. Should we qualify firmware embedded in the equipment hardware?
6. How should the computer and software part of a system be tested?
7. How frequently should the OQ tests be done?
8. Should the tests be redone after instrument upgrade, after a repair, or when the instrument is moved to another lab?

9. Can or should the test be done by the vendor or by the user?
10. Can or should preventive maintenance be performed before the OQ test?
11. Why is OQ needed? If the equipment is used for one specific application only, isn't PQ enough?

In this chapter, the author gives recommendations related to the OQ of equipment hardware. OQ of software and computer systems is discussed in Chapter 10.

CONSIDERATIONS

What Should Be the Test Items, Procedures and Acceptance Limits?

Before starting a discussion related to test items, test procedures and acceptance criteria, we should have a closer look at the OQ definition created by the LGC/EURACHEM working group (30):

> *The process of demonstrating that an instrument will function according to its operational specification in the selected environment.*

Another similar definition for OQ came from the U.S. PMA (71):

> *Documented verification that the equipment related system or subsystem performs as intended throughout representative or anticipated operating ranges.*

Although this definition is brief and leaves a lot of room for interpretation, one thing becomes obvious: 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, yet many operators prefer to use the manufacturer's specifications because usually these are readily available.

However, a mistake such as this can have an enormous impact on the equipment's maintenance costs. One example is the baseline noise of a UV/visible detector, a performance criterion that is important for a method's limit of detection and limit of quantitation.

The baseline noise as offered today by many UV/visible detectors is in the range of 1 to 2×10^{-6} absorption units (AU) and much lower than

the limits of detection and quantitation required for most applications. This value is achieved under optimum conditions, such as with a reasonably new lamp, an ultra-clean flow cell, stable ambient temperature, HPLC grade mobile phase, no micro leaks in the entire HPLC system, and so on. These conditions are always valid at the manufacturer's final test and probably at the time of installation in the user's laboratory. However, after some time, optical and mechanical parts deteriorate (e.g., the lamp loses intensity and the flow cell may become contaminated). So, if we repeat the test after 3, 6, or 12 months, the noise of $1 - 2 \times 10^{-6}$ AU may no longer be obtained.

The question now is: How do we know when the detector was not within the OQ specifications? An auditor also may ask the question: How do we know that all the data measured in the past are valid if the instrument was not within the specifications as set by the user? In this case, it is therefore necessary to perform the OQ tests much more frequently, and to change the lamp more frequently, and probably clean the flow cell on a regular basis. This requires additional operator time and creates additional costs, which can be justified if the application requires low baseline noise. They cannot be justified if the instrument is used only for applications that don't require low baseline noise.

There is no question that a user can as a normal business practice insist that an instrument meets published vendor specifications at the time of a new installation and can refuse the bill if it does not, but this should not be mixed up with a regulated activity that can have other consequences.

Which Test Sample Should Be Used: A Generic Standard or a Standard That Is Specific to the Application?

Let's assume the instrument is used for different applications, which require different samples, different columns, and different calibration standards. In this case, it is recommended to use a generic standard for the same instrument category. It is also recommended to use 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.

Should All Instruments of the Same Category Meet the Same Criteria or Should Each Instrument Have Its Own Limits?

This is another question that comes up frequently in discussions. For example, you have in your lab HPLC systems from different vendors that may also have been purchased at different times. In this case, the instruments will have different performance characteristics. For example, the UV/visible detector's baseline noise has decreased by about a factor of 10 over the last 10 years. There may be instruments in the lab with 2×10^{-5} AU and others

with 2×10^{-6} AU. The recommendation is to define 4×10^{-5} AU as a general limit. If there are applications on specific instruments that require a lower baseline noise, select the newer ones to be run for this application, and make an exception for the noise limit for this instrument, 5×10^{-5} AU, for example.

How Often Should OQ Be Performed?

Test frequency is another important question. Should it occur once a month, after several months or once a year? The answer depends on the

- type of equipment,
- usage of the equipment,
- nature of usage (environment, application),
- stability of the equipment, and
- operational specifications set by the user.

The most important criterion here is to make sure that the test frequency selected will result in a high probability that the equipment will pass the tests.

Should Firmware be Qualified?

Firmware is software that is embedded in a hardware device. It is often provided on flash ROMs or as a binary image file that can be uploaded onto existing hardware by a user. There are arguments that firmware should be qualified because the structure of the code is comparable with software. Firmware is used to control instrument parameters, to serve as an interface to computer systems, and to automate instruments which is similar to hardware. Typically the code is not accessible to the user and equipment hardware cannot be tested without proper functioning of the firmware. There is general consensus that firmware in analytical instruments does not need to be tested in addition to or separated from hardware. The revision of the firmware should be documented and kept under version control. Firmware upgrades should follow change control procedures and should be recorded. This should also be clearly communicated to vendor's technicians. The need for partial or full requalification of equipment hardware after firmware upgrades should be assessed. Instrument suppliers should provide information on what the changes are and how they can impact the qualification status of the instrument.

Modular versus Holistic Testing

Another frequent point for discussion used to be whether each individual module in a system should be tested (modular testing) or if the system should

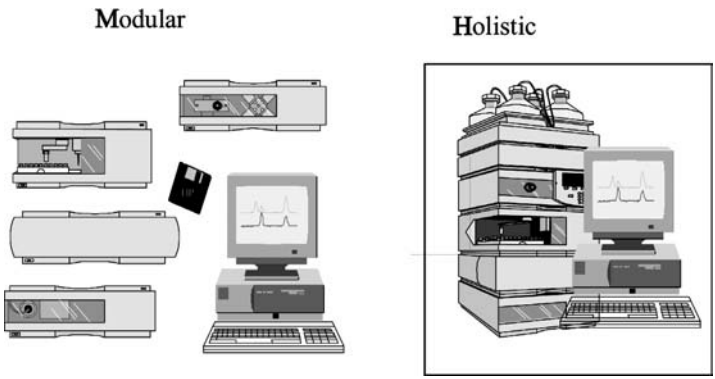


Figure 1 Modular vs. holistic testing.

be tested as a whole (holistic testing) (Fig. 1). This discussion was suddenly halted by a statement published by a U.S. FDA field investigator (108). The recommendation was, and still is, to generally use the holistic approach; test the system as a whole, and look into individual modules only if the system does not pass. However, this approach is more applicable for diagnostic purposes than for test purposes. The same recommendation has been made by the LGC/EURACHEM working group (30).

Who Should Perform the Test—a Representative of the Vendor or the User?

Testing performance involves both resources and economics, in addition to the technical aspects of the test. In principle, testing can be done by both the user and the vendor. The technical question relates to the procedure the vendor offers: Does it really check the critical performance limits of the instrument? As long as test procedures relate to the intended use of the instrument, it may be more economical if a vendor does them. 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 a calibration stamp on the equipment that comes from outside the user's lab.

Should Preventive Maintenance Be Done Before OQ?

In our example with the UV/visible detector lamp, preventive maintenance would solve the problem of not being within specifications due to the lamp aging. The LGC/EURACHEM working group recommends performing preventive maintenance before OQ; the only problem is that in this case there is no evidence that the instrument was performing properly at all times. This issue may also come up during an inspection. 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 tasks? The answer to this question will also answer the preventive maintenance question. In light of this, the exact purpose of OQ should be included in the operating procedure.

Should the Tests Be Redone after Maintenance, Upgrade, or Repair (Requalification)?

Whenever something has occurred with the equipment, be it a repair or an upgrade, the correct functioning and performance of the system should be verified through appropriate tests. This procedure is widely referred to as *requalification.* The type of tests depends on the type of repair or upgrade. For example, if an autosampler of an HPLC system has been repaired, the performance characteristics influenced by the autosampler should be tested for the injection volume precision and the carryover. There is no need to perform the pump's gradient accuracy or the detector's linearity. Instrument vendors should provide a list with recommendations for each system and module on what should be tested after a repair or a system upgrade. The tests used for requalification should be designed so that the results can be compared with those obtained from the initial qualification. Any significant differences in the results obtained from old and new tests should be identified, recorded, and resolved.

What Should Be Done If a Module Is Replaced on a Modular System?

Sometimes complete modules are replaced either because a new application may require a new detector or because the old one is defective. In this case, all detector specific system tests, such as baseline noise, detector linearity, or the wavelength accuracy of an HPLC UV detector, should be performed. It is not necessary to check other module parameters, such as the step gradient accuracy of the pump.

Should the Tests Be Redone When the Instrument Is Moved?

The retesting of equipment after it has been moved depends on the type of equipment and extent of movement. If the instrument is moved along a bench, no requalification is required for most instruments. For equipment with mechanical susceptibility to vibrations, part of the requalification is required. For example, for an HPLC system with a UV variable wavelength detector with a motor-driven grating, the wavelength accuracy should be verified. Similarly, if a balance is moved, it should be recalibrated. The situation is similar if the equipment is moved within a laboratory to another bench. If the instrument is moved to another laboratory within the same building or to another

building with different environmental conditions, a full requalification should be performed. The decision if and what to test after the movement should be based on science and on a justified and documented risk assessment. Always think about the inspector's question: How can you be sure that the instrument did perform as intended after the movement?

What Should Be Done When the Instrument Is Used for Another Application?

If the application is similar and all OQ tests and acceptance criteria are covered through the initial OQ, no additional tests are required. If the new application has different or additional demands, which are not covered through the initial application, appropriate OQ tests should be done. For example, if for a chromatographic analysis the instrument initially was used for high concentrations with no need for baseline noise tests, such tests should be done if the new application requires the analysis of trace compounds. Other performance tests, such as the precision of the injection volume, are not required in this case.

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; isn't PQ 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. If the instrument is used for just 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. The critical issue here is which parameters are tested within the PQ test.

One should also not forget that regular OQ tests provide ongoing information on the performance of the HPLC system. Performance trends can be measured and recorded and can also give an early indication that an instrument may no longer perform as expected in the near future. For example, gradient composition precision is a key factor for the precision of peak retention times and, therefore, peak areas. If this parameter is measured and approaches the limit, the peak retention time precision will also soon exceed the specified limits.

DOCUMENTATION

The documentation of testing should include:

- the description and unique identification of equipment,
- test items,

- acceptance criteria,
- actual results,
- date when the test was performed, and
- names and signatures of persons who performed the tests.

If the tests were performed by a manufacturer's representative, the test report should be signed by the vendor's and the user's representative. The instrument should be labeled with the calibration and qualification status indicating the dates of the last and next calibration and OQ.

A PRACTICAL AND ECONOMICAL APPROACH FOR IMPLEMENTATION

Several qualification aspects were discussed in the previous chapter. Now it is relevant to give recommendations for practical implementation.

1. Use only one documented procedure for all instrument categories of the same type in your lab, preferably within your company. This significantly reduces the number of documents and time for training of personnel. This also allows you to compare performance of instruments from different vendors, different model numbers, and at different sites.
2. For all instrument categories in a laboratory (gas chromatographs, for example), use the same OQ procedure and the same test compounds. This makes it easy to compare instruments against each other; new instruments can be compared with existing ones, and it is easier to set specifications for future purchases.
3. For all instruments in a laboratory, use the same acceptance limits, independent of the age, brand, and actual performance of the instrument.
4. The procedures and the acceptance limits should be selected so that in normal circumstances all instruments pass the test. Therefore, the instrument with the worst performance will determine the acceptance limits.
5. If there are applications on specific instruments that require more stringent performance limits for specific applications, make an exemption of this instrument, and set the limits to the more stringent value.
6. Define the time distance between two OQs so that the instrument will pass the test with high probability.

7. Decide and document if preventative maintenance should be done before OQ tests. If the preventive maintenance is done before OQ, think about an answer to the question: How can you be sure that the instrument was performing as intended before the maintenance?
8. In case OQ is for future use, plan preventive maintenance before OQ.
9. Always start with the test of the full system (holistic testing). If that test does not meet the criteria, test individual modules to identify the module that caused the problem.
10. Make a technical and operational evaluation on whether to do OQ using your own staff or the vendor's representatives. If the vendor's procedure does not deviate greatly from your expectations, ask if the vendor can make adjustments.
11. Always ask the vendor for help. Even if you decide to do OQ using your own staff, the vendor should still assist you by providing test procedures, certified standards for testing, and software for automated testing.
12. Generate a test report that includes a table with test items, your acceptance criteria, actual results, and whether or not the test met the criteria. An example is shown in Figure 2. Keep this report for regulatory purposes.

Summary Recommendations

1. Develop an operating procedure for OQ.
2. If the vendor offers OQ services, make an economic evaluation on whether OQ by the vendor or the user's firm will be more cost-effective.
3. Use generic chemical standards for testing if the equipment will be used for several different applications. Use an application specific standard if the instrument will be used for one application only.
4. If there are multiple instruments of the same category in a lab, use the same procedure and acceptance limits for all instruments.
5. Set the acceptance limit higher than the manufacturer's specification. This may be up to a factor of 5 or 10. For those instruments that require more stringent values to demonstrate their fitness for the intended use, an exception should be made, and the limits should be set to more stringent values.

HPLC Instrument Verification Report

Test method:	C\HPCHEM\1\VERIF\Check.M
Data File Directory:	C\HPCHEM\1\VERIF\Result.D
Original Operator	Dr. Watson

Test item	User limit	Actual	Com
DAD noise	<5x10-5AU	1x10-5AU	Pass
Baseline drift	<2x10-3AU/hr	1.5x10-4AU/hr	Pass
DAD WL calibration	±1 nm	±1 nm	Pass
DAD linearity	1.5 AU	2.2 AU	Pass
Pump performance	<0.3 % RSD RT	0.15 % RSD RT	Pass
Temp.stability	±0.15 °C	±0.15 °C	Pass
Precision of peak area	< 0.5% RSD	0.09 % RSD	Pass

Verification Test Overall Results Pass
HP 1100 Series System, Friday, January 16, 1998
Test Engineer
Name: Signature:

Figure 2 Operational qualification report with test item, user limit, and result.

6. For modular systems, test the system as a whole, not module by module.
7. Set the time intervals between two OQs so that the actual test results in general are at least 30 percent away from the limits.
8. Chemical standards used for instrument calibration or qualification tests should be traceable to national standards. If the system is intended to be used for different analytical methods, a generic chemical standard with known stability should be used. If the system does not perform as expected, individual modules may be recalibrated and interchangeably used to identify the source of the system problem; thus, modular testing is recommended for troubleshooting purposes.

9

Performance Qualification and Maintenance

What Is Discussed in this Chapter?

1. Procedures to ensure ongoing equipment performance
2. Content of an instrument logbook
3. Type and frequency of performance testing
4. Frequency and parameters for system suitability testing
5. Development and interpretation of QC charts
6. Procedures for error handling

DEFINITION

Performance qualification (PQ) is the process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use (30).

The important words in the definition of PQ are *consistent* and *for its routine use*. The test frequency is higher than for OQ. Another difference is that PQ should always be performed under conditions that are the same as, or similar to, those for routine sample analysis. For a chromatograph, this means using the same column, the same analysis conditions, and the same or similar test compounds and sample matrices.

As shown in earlier chapters, validation and qualification are not single occurrence events; they should be performed over the entire life of the equipment. During routine use, procedures should exist to demonstrate that the equipment will continue to do what it purports to do. In simple words, PQ should answer this question: How can you be sure that the system works as intended day-by-day? Testing should not be the only activity to ensure

ongoing reliable data. Preventive maintenance, ongoing training for new operators, regular security checks for computer systems, and an appropriate error detection system are equally important. Each laboratory should have a comprehensive QA program that is well understood, accepted, and followed by individuals, as well as by laboratory organizations, to prevent, detect, and correct problems. The purpose of this program is to ensure that the equipment is running without problems and that analytical results have the highest probability of being of acceptable quality. Ongoing activities may include the following:

1. Preventive instrument maintenance
2. Regular calibration
3. Full or partial OQ checks
4. Daily check of critical performance characteristics, for example, baseline noise of a UV detector if limit of detection is critical
5. Daily system suitability testing
6. Analysis of blanks
7. Duplicate analysis
8. Analysis of QC samples
9. Procedures to detect, record, and handle errors and other unforeseen events
10. Regular security checks
11. Changes to the system in a controlled manner and controlled requalification after the change, if necessary
12. Internal audits
13. Participation in proficiency testing schemes
14. Ongoing training programs for employees

Items 1 to 9 are specific to measurements and are, therefore, covered in this chapter. Internal audits, people qualification, and proficiency testing affect many other activities and will be discussed in three separate chapters. The frequency and need for PQ activities should be based on the type of equipment, the instrument's application, and previous experience with the equipment and should be documented in in-house procedures. Daily system tests as required by pharmacopeias or quality standards should be part of PQ testing. Examples are system suitability tests and the analysis of quality control samples. In many cases they are enough proof that instruments are suitable for intended use and no additional tests are required. However, this would assume that the tests are designed such that they test all critical parameters. For example, if a system is used for quantitative trace level analysis, one test should be designed for this application.

All calibration and maintenance activities, errors, repairs, performance tests, and other events should be recorded in a logbook. This chapter therefore begins with the organization and content of an equipment logbook.

LOGBOOK

For each instrument, a logbook should be prepared for operators and service technicians to record all equipment-related activities in chronological order. The logbook must be readily available near the equipment, for example, in a drawer next to the instrument or attached to the instrument itself. Information in the logbook may include the following:

- Logbook identification (number, valid time range)
- Instrument identification (manufacturer, model name/ number, serial number or reference to the IQ document with serial numbers, firmware revision or reference to the IQ document with firmware revisions, date received, service contact)
- Column entry fields for dates, times, and events, for example, initial installation and calibration, module and system updates, errors, repairs, performance tests, QC checks, cleaning and (preventive) maintenance, as well as fields for the name and signature of the technician making the entry.

  Events that have involved a repair should always include

- the observed symptom,
- what was repaired, and
- what was tested after the repair.

Currently, the most convenient format for such a logbook is a bound paper book format or a 2- or 3-ring binder where forms can easily be added. There is also a clear trend toward the use of electronic notebooks. Some instruments even have such notebooks included to enable information to be entered on a local instrument controller or computer. The logbook should be archived together with calibration and analyses data. Figure 1 shows an example of an extract from a logbook of an HPLC system.

Application-specific items that are part of the analysis system but frequently changed should not be documented in the instrument logbook; they should be recorded on the daily run sheet for sample runs on that particular system. Examples of this are analytical columns and guard columns.

A well-organized logbook can help to identify possible sources of data errors that have occurred at any specific time. It also helps to identify the expected life span of maintenance parts.

The key to success of any logbook is for it to be used by the operators. Availability of the logbook close to the instrument and a clear structure with easy-to-enter fields for entries will help to achieve this.

Logbook ID, valid from:	HPLC 14, valid from June 17, 2006
Name of equipment:	Liquid Chromatograph with ChemStation
Manufacturer:	Agilent
Model:	HP1100 Series
Serial numbers:	See IQ document of HPLC System A3
Service contact:	Agilent xxxx-xxxxx

Date	Event	Name	Signature
3/7/06	*Lamp intensity below acceptable limit; exchanged lamp on UV-detector, (P/N 4523-6784); measured intensity profile; measured baseline noise*	*K.Weber*	*K.Weber*
12/10/06	*System suitability tests results showed retention time precision above limit; pump seal changed, (P/N 1056-5349); performed system suitability test*	*K.Weber*	*K.Weber*
07/11/06	*Installed new HP DeskJet printer on ChemStation; performed ChemStation performance verification*	*M.Bauer*	*M.Bauer*
04/12/06	*Exchanged Agilent 1100 UV detector; performed lamp intensity, wavelength accuracy, baseline noise and baseline drift tests. All tests passed specifications. For details see the qualification workbook.*	*M. Bauer*	*M.Bauer*
Page 3			

Figure 1 Extract from an HPLC instrument logbook. *Abbreviation*: HPLC, high performance liquid chromatography.

MAINTENANCE

Operating procedures for maintenance should be in place for every system component that requires periodic calibration and/or preventive maintenance. Preventive maintenance of hardware should be designed to detect problems

before they occur. Critical parts should be listed and be available at the user's site. The procedure should describe

- the maintenance to be done,
- when is it to be done,
- what should be tested afterwards, and
- the necessary qualifications for the engineer performing the tasks.

The system components should be labeled with the dates of the last and next scheduled maintenance. All maintenance activities should be documented in the instrument's logbook. Suppliers of equipment should provide a list of recommended maintenance activities and documented procedures on how to perform the maintenance. They also should provide a list with recommended test procedures after maintenance activities. Some vendors also offer maintenance contracts with services for preventive maintenance at scheduled time intervals. A set of diagnostic procedures is performed and critical parts are replaced to avoid or identify problems that have not yet reached the point where they may have an impact on the proper functioning of the system.

Traditionally, maintenance parts are replaced on a set time basis. For example, an HPLC pump seal is replaced every six months, a detector's lamp every three months or so. This is neither economical for the laboratory nor environmentally friendly because frequently the parts would not necessarily need to be exchanged at that particular time. It is better to exchange maintenance parts on a usage basis, as implemented on Agilent's HPLCs through the early maintenance feedback (EMF). The user can enter set limits for the lamp, the solvent pumped through, and the number of injections. The instruments record the time usage; if the limits are exceeded, the user is informed via the user interface. This allows timely exchange of the maintenance parts before instrument performance drops below the acceptable limit. The elapsed time after which maintenance should be carried out depends on the particular application. For example, the time after which an HPLC pump seal should be exchanged depends on the mobile phase. The lamp life of an HPLC UV detector depends on the level of baseline noise that is still tolerable for a specific application. The best usage time for a specific part and application should be taken from experience.

CALIBRATION

After a certain period of time, operating devices may require recalibration if they are not to impact adversely the performance of an instrument (e.g., the

Instrument	BestBalance	
Serial number	55235A	
Maximal weight	110 g	
Control weight 1	10,000 mg	Limit +-10 mg
Control weight 2	1,000 mg	Limit: +-1 mg
Control weight 3	100 m	Limit: +- 0.1 mg

Date	Weight 1	Weight 2	Weight 3	o.k.	Test engineer Name	Signature
2/5/06	9999.8	999.9	100.0	yes	Hughes	

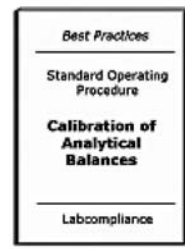


Figure 2 Results of calibration are entered on forms.

wavelength of a UV-visible detector's optical unit or a balance). A calibration program should be in place to recalibrate critical instrument components following documented procedures, with all results recorded in the instrument's logbook. The system components should be labeled with the date of the last and next calibration. The label on the instrument should include the initials of the test engineer, and the calibration report should include his or her printed name and full signature. It is recommended to use forms for instrument calibration, with entry fields for instrument type and serial number, the test frequency, the expected value and acceptance limits, and the date and results of actual measurements. An example is shown for an analytical balance in Figure 2.

PERFORMANCE TESTING

The characteristics of equipment alter over time due to contamination and general wear and tear. HPLC UV detector flow cells become contaminated, pump piston seals abrade, and UV detector lamps lose intensity. These changes have a direct impact on the performance of analytical hardware and may have a negative effect on the analytical data; therefore, the performance of analytical instruments should be tested during routine use. The CITAC/ERACHEM *International Guide to Quality in Analytical Chemistry*

(31) specifies the need for performance checks in addition to maintenance and calibration:

> *Correct use combined with periodic servicing, cleaning, and calibration will not necessarily ensure an instrument is performing adequately. Where appropriate, periodic performance checks should be carried out (for example, to check the response, stability and linearity of sources, sensors and detectors, the separating efficiency of chromatographic systems, the resolution, alignment and wavelength accuracy of spectrometers, etc.).*

The performance of equipment should be tested on a frequent basis, for example, daily or each time the instrument is used. The test frequency depends not only on the stability of the equipment but on everything in the system that may contribute to the analysis results. For a liquid chromatograph, this could, for example, be the chromatographic column. 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 to documented, preset limits. Aspects of PQ are often built into analytical methods or procedures. This approach is often called system suitability checking (SSC) and demonstrates that the performance of the measuring procedure (including instrument operating conditions) is appropriate for a particular application. For example, a well-characterized standard may be injected five or six times, and the standard deviation of amounts is subsequently compared against a predefined value. The analysis of QC samples, together with the measurement of certain critical performance characteristics (for example, a detector's baseline noise for trace level analysis) is also suitable and may be sufficient for PQ measurements. Table 1 includes six steps that can be carried out during preparation and PQ itself.

The user of the equipment carries full responsibility for these activities. The supplier can provide recommendations on what to check, the procedures with test conditions, recommendations for performance limits (acceptance criteria), and recommended actions in case criteria are not met. PQ should follow documented procedures.

Which performance characteristics should be tested, and how often? A recommendation on the frequency of performance checks is given in the CITAC/EURACHEM guide (31).

> *The frequency of such performance checks will be determined by experience and based on need, type, and previous performance of equipment. Intervals between the checks should be shorter than the time the equipment has been found to take to drift outside acceptable limits.*

This interpretation means that the frequency of performance checks for a particular instrument depends on the acceptable limits specified by the user. The more stringent the limits, the sooner the instrument will drift out of them, thus increasing the frequency of the performance checks. The time interval between checks should be identified by experience and documented for each instrument.

Appendix B of the CITAC guide (31) lists parameters to be checked for chromatographic instruments, including liquid and ion chromatographs; for heating/cooling apparatus, including freeze-dryers, freezers, furnaces, hot-air sterilizers, and incubators; and for spectrometers, autosamplers, microscopes, and electrodes. The frequency of checks for other equipment, including balances, volumetric glassware, hydrometers, barometers, timers, and thermometers is also listed.

A good recommendation is to carry out performance checks more frequently for new instruments. If the instrument continually meets the performance specifications, the time interval can always be increased.

SYSTEM SUITABILITY TESTING

The mechanisms proposed to prove that systems perform as expected for their intended use are system suitability tests or the analysis of QC samples by constructing control charts. It is recommended that users perform the checks once a day, or even more frequently, depending on the stability of the system and the number of samples analyzed daily.

System suitability tests have been proposed and defined for chromatographic systems by the USP and other pharmacopeias. Compared to method validation or instrument operational qualification, daily system suitability

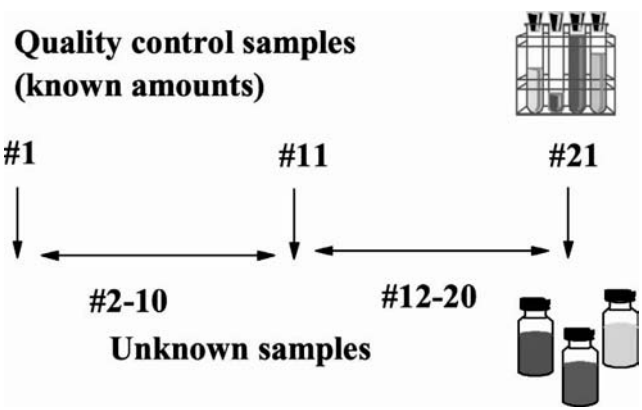


Figure 3 For an accurate quality check, quality control (QC) samples are interspersed among actual samples.

Table 1 Steps for Performance Qualification

1. Define the performance criteria and test procedures. These may derive from OQ tests or from analytical methods or procedures.
2. Select critical parameters. For a chromatography system these could be
   - a detector's baseline noise,
   - precision of the amounts,
   - precision of retention times,
   - resolution between two peaks,
   - peak width at half height, or
   - peak tailing.
3. Select acceptance criteria.
4. Define test intervals, e.g.,
   - every day;
   - every time the system is used;
   - before, between, and after a series of runs;
   - for a long sequence of runs: 5% of all runs.
5. 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.
6. Perform tests as specified in step 1 and at intervals as specified in step 4; check the results against the acceptance criteria as specified in step 3 and take corrective actions, if necessary, as specified in step 5.

testing requires fewer individual determinations. A general recommendation is to check those parameters that are critical to analysis accuracy and that may change over a relatively short time. The exact type and frequency of tests should be defined during method validation. As a minimum requirement for compound analysis for chromatographic systems, the USP (51) recommends the following measurements:

- Precision of peak areas (system precision)
- Resolution between two compounds
- Tailing factor

Baseline noise and drift and precision of retention times are other possible parameters necessary, for example, when the detection limit or the stability of retention times is critical to the analysis.

System precision is determined by repeatedly injecting a standard solution and measuring the relative standard deviation of the resulting peak areas

or peak heights. For the USP monographs (51), unless otherwise noted, 5 replicate chromatograms are required when the stated relative standard deviation (RSD) is 2% or less. For values greater than 2%, 6 replicate chromatograms should be used. For bioanalytical samples, the percentage RSD should not exceed 15%, except at the limit of detection where it should be less than 20% (51).

Quality Control Samples with Control Charts

The analysis of QC samples by constructing control charts has been suggested as a way to incorporate quality checks on results as they are being generated. Such tests can then flag the values that may be erroneous for any of the following reasons:

- Reagents are wrongly mixed
- Reagents are contaminated
- GC carrier gas is impure
- HPLC mobile phase is contaminated
- Instrument characteristics have changed over time
- Operators are not sufficiently trained

For an accurate quality check, QC samples are interspersed among the samples themselves at intervals determined by the total number of samples and the precision and reproducibility of the method (Fig. 3). The control sample frequency depends mainly on the known stability of the measurement process; a stable process requires only occasional monitoring. The CITAC/EURACHEM guide (31) states that 5% of sample throughput should consist of QC samples for well-established routine analysis and up to 20% for more complex procedures.

Control samples should have a high degree of similarity to the actual samples analyzed; otherwise, one cannot draw reliable conclusions on the measurement system's performance. Control samples must be so homogeneous and stable that individual increments measured at various times have less variability than the measurement process itself. QC samples are prepared by adding known amounts of analytes to blank specimens. They can be purchased as certified reference materials or may be prepared in-house. QC materials based on environmental matrices, food, serum, or urine are commercially available for a variety of analytes. For day-to-day routine analysis, it is recommended to use in-house standards that are checked against a certified reference material. Sufficient quantities should be prepared to enable the same samples to be used over a longer period of time. Their stability over time should be proven, and their accuracy verified, preferably through a

comparison with a certified reference material, through interlaboratory tests or by other analysis methods.

The most widely used procedure for the ongoing control of equipment, using QC samples, involves the construction of control charts. These are plots of multiple data points versus the number of measurements from the same QC samples using the same processes. Measured concentrations of a single measurement, or the average of multiple measurements, are plotted on the vertical axis, with the sequence number of the measurement on the horizontal axis. Control charts provide a graphic tool to

- demonstrate statistical control,
- monitor a measurement process,
- diagnose measurement problems, and
- document measurement uncertainty.

Many schemes for the construction of such control charts have been put forward. This book has only limited scope for describing control charts and the statistical theory on which they are based. Details on how to collect data and on how to construct Shewhart control charts are described in the ISO Guides 7870 (72) and 8258 (13).

The most commonly used control charts are X charts and R charts, as developed by Dr. Walter Shewhart in 1924 (13). Both charts are often plotted together as X/R charts. R charts plot the range of results obtained from two or more measurements. This shows any change in the dispersion of the process. X charts either plot single results points for single measurements or the average values from multiple measurements. They consist of a central line representing either the known concentration or the mean of 10 to 20 earlier determinations of the analyte in a control material (QC sample). The standard deviation, determined during method validation, is used to calculate the control lines in the control chart. Control limits define the bounds of virtually all values produced by a system in statistical control.

X charts (Fig. 4) often have a center line and two control lines with two pairs of limits: a warning line at $m \pm 2\sigma$ and an action line at $m \pm 3\sigma$. Statistics predict that 95.45% and 99.7% of the data will fall within the areas enclosed by the $\pm 2\sigma$ and $\pm 3\sigma$ limits. The center line is either the mean or the true value. In the ideal case, where unbiased methods are used, the center line is the true value. This applies, for example, to precision control charts for standard solutions.

When the process is under statistical control, the day-to-day results are normally distributed about the center line, and 1 out of 20 results is expected to fall between the warning and action lines. No action is required if only one result falls in this area, provided that the next value is inside the warning

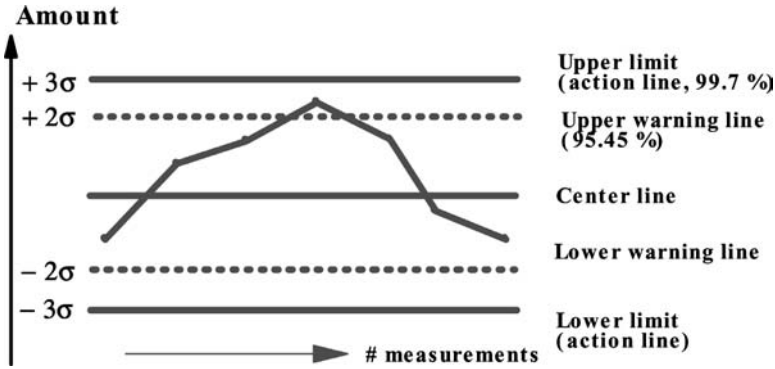


Figure 4 Quality control chart with warning lines and control lines.

line. However, if two consecutive values fall between the warning and action lines, then there is evidence of loss of a statistical control. Seven or more consecutive points above the 50 percent confidence limit indicates a tendency for the process to get out of control. More out-of-control situations are shown in Figure 5. In these cases, the results should be rejected and the process investigated for its unusual behavior. Further analyses should be suspended until the problem is resolved. Instruments and sampling procedures should be checked for errors.

QC samples may have to be run in duplicate at three concentrations corresponding to the levels below, within, and above the analysis range. For methods with linear concentration–response relationships over the full analysis range, two concentrations, one each at the high and low end of the range, are adequate.

An ideal control sample should simulate sample compounds and sample matrices as closely as possible. Other criteria for control samples are

- safe to use for the laboratory staff,
- stable over time,
- long lasting,
- cost-effective, and
- traceable to any national or international standards, if such standards are available.

In routine analytical analysis, the control sample amounts are typically plotted versus the sample number as quality characteristics. This is a useful measurement because it indicates what may come up during sample preparation and measurement. In chromatography, other control parameters may

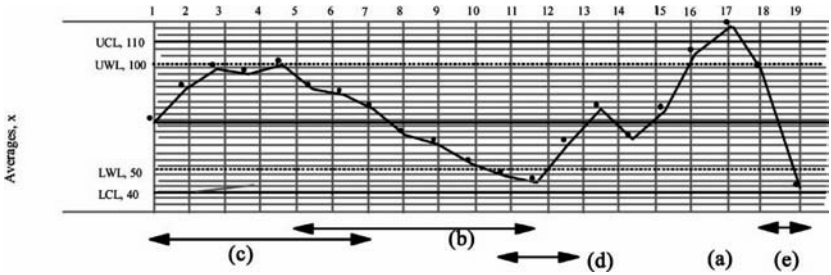


Figure 5 Possible out-of-control events. (A) one value outside the control limit. (B) seven consecutive values ascending or descending. (C) seven consecutive values above or below the center line. (D) two out of three consecutive values outside the warning limits. (E) difference between 2 consecutive values >4 s.

be considered, for example, the resolution between two peaks, the width of a specific peak at the half-peak height, or the tailing factor (Fig. 6). Measuring and plotting these parameters gives useful hints when the system approaches the limits of specified ranges, and corrective actions can be initiated before wrong data are measured. For example, if in liquid chromatography the resolution between two peaks drops below a specified limit, or the tailing factor goes above a certain limit, it is most likely that the column needs to be changed.

A documented quality procedure should be in place that provides the operator with step-by-step instructions in the event that the results of one or more QC samples are outside the warning or control line. There are two types of corrective action: immediate on-the-spot and long-term. On-the-spot action is used to correct minor problems, such as the replacement of defective instrument parts, for example, an HPLC UV-visible detector lamp. These actions can be performed by a single individual, and analytical methods or procedures do not need to be changed. Long-term action is required when

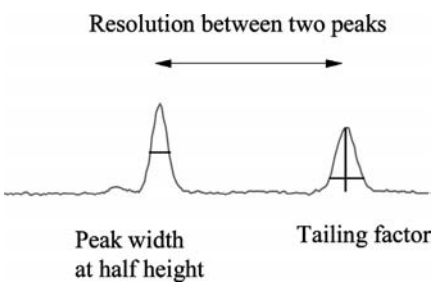


Figure 6 Possible quality characteristics in chromatography.

Table 2 Possible Actions in Out-of-Control Events

Check materials (reagents, solvents, and calibration standards for correct weighing, within specified time for stability, different supplier?)
Check QC sample (correct weighing, storage conditions, within stability time?)
Check if the right method has been used
Check instrumentation (hardware, software, correct integration, sufficient separation, sufficient precision?)
Check whether the operator changed

an out-of-control situation (Table 2) is caused by a method, an uncommon equipment failure, or laboratory environment problem.

For long-term actions, one person is made responsible for investigating the cause, developing and implementing corrective action, and verifying that the problem has been solved.

HANDLING OF DEFECTIVE INSTRUMENTS

Clear instructions should be available to the operator on actions to take in the event that an instrument breaks down or fails to function properly. Recommendations should be given on when operators should attempt to rectify the problem themselves and when they should call the instrument vendor's service department. In cases of malfunction, it is not sufficient to repair the

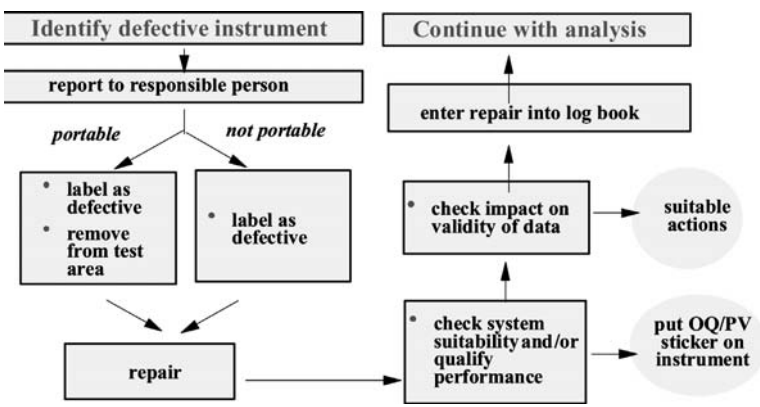


Figure 7 Handling of instruments with uncommon failures. *Source*: Ref. 53.

instrument on-site and then to continue performing analyses. For each instrument, there should be a list of common and uncommon failures, and every problem should be classified in this way (Fig. 7). Common problems, such as a defective UV-visible detector lamp, require short-term action. The lamp should be replaced and, after a functional test, the instrument can be used for further analyses. The failure, repair, and result of the functional test should be entered into the instrument's logbook.

In the case of an uncommon failure that cannot be easily classified and repaired by the operator, several steps are required.

- The problem should be reported to the laboratory supervisor, or to the person responsible for the instrument, who will decide on further action.
- The instrument should be removed from the laboratory and stored in a specified area or, if this is impractical due to its size, it should be clearly labeled as being defective. For example, portable equipment such as pH meters should be removed, while larger equipment such as an HPLC, a GC, or an ICP-MS system should be labeled "out of service."
- After repair, correct functioning must be verified, as well as the type and extent of testing depending on the failure and possible impact on the system. Depending on the failure, this may require part or full performance verification (requalification) or only system suitability testing.
- The impact of the defect on previous test results should be examined.
- Clients should be info rmed about the effect the failure may have had on the validity of their data.
- An entry on the defect, repair, and performance verification should be made in the instrument's logbook.
- The need for preventive action should be evaluated to prevent re-occurrence of the same problem on the same or similar instruments.

Summary Recommendations

1. Develop an equipment logbook.
2. Develop maintenance procedures (with the help of the vendor).
3. Develop procedures and acceptance limits for performance testing (criteria: regulations, instrument type, application, performance requirements).

4. Regularly perform system tests, e.g., system suitability tests or analysis of quality control charts.
5. Develop procedures in case acceptance criteria are not met.
6. Develop procedures in case of equipment failures.

10

Special Considerations for Software and Computer Systems

What Is Discussed in this Chapter?

1. Regulatory requirements for laboratory computers
2. How to classify different categories of computer systems in laboratories
3. How to validate computerized analysis systems
4. How to qualify computer networks
5. How to validate user-contributed software programs (e.g., macros)
6. How to validate existing systems
7. Validation for 21 CFR Part 11
8. What documentation should be generated

INTRODUCTION

Computer systems are widely used in analytical laboratories for instrument control, data acquisition, data evaluation, document generation and archiving, and information management. The correct functioning of software and computer systems should be verified after installation and before and during routine use. Regulatory agencies pay much attention to the validation and use of computers in the regulated environment. For example, the EU guide to GMP has an appendix focusing on using computers in GMP environments (41). FDA regulation for electronic records and signatures (42) requires validation of computer systems used in FDA-regulated environments and the OECD GLP consensus paper number 10 (58) requires acceptance testing, which is part of an OQ. Furthermore, PIC/S has published a 55-page good practices guide on using computers in GxP environments (21).

Several industry organizations have developed guidance documents for computer validation. Most important references are the GAMP 4 (61), which is the reference document for computer validation, and a Good Practices Guide on the Validation of Laboratory Computerized Systems (7), which is specifically important for laboratories.

The subject of computer validation has also been widely discussed by private authors and a detailed coverage of the subject would fill several books. In this chapter we give a brief overview on how to handle software and computer systems in laboratories. More details on the overall validation of software and computerized analytical and networked systems can be found in a book dedicated to this subject (73).

Validation of software and computer systems is more difficult than for hardware for five reasons:

1. It is more difficult to define specifications for software.
2. It is more difficult to define test procedures and acceptance criteria.
3. With the increasing use of networks, computer systems get more and more complex.
4. Frequently, software used in laboratories has not been designed for and does not have the functionality that enables users to comply with regulations.
5. While equipment hardware performance problems are easily identified, this is not always the case with software. Even though they may be present from the start, they may become evident only after certain combinations of software modules are executed.

LIFE CYCLE CONSIDERATIONS

As described in Chapter 3 of this book, qualification of equipment happens in phases that are documented in a life-cycle model. While the 4Q model as described is ideal for commercial equipment without customization by the user, it does not address equipment developed by the user. It also does not address the situation when equipment is purchased from a vendor and customized. However, this situation frequently happens with computer systems. Commercial systems are bought from a vendor and the users add software either developed by the user or by a third party specifically for the user. An example is a VBA script for a spreadsheet such as Excel.

For this situation, a life-cycle model that combines system development and system integration is preferred. Such a model has been described by GAMP (7) that combines system integration and system development. A modified version is shown in Figure 1. User representatives define User or System Requirement Specifications (URS, SRS). Software or systems developed by or for a specific user follow the development on the left side.

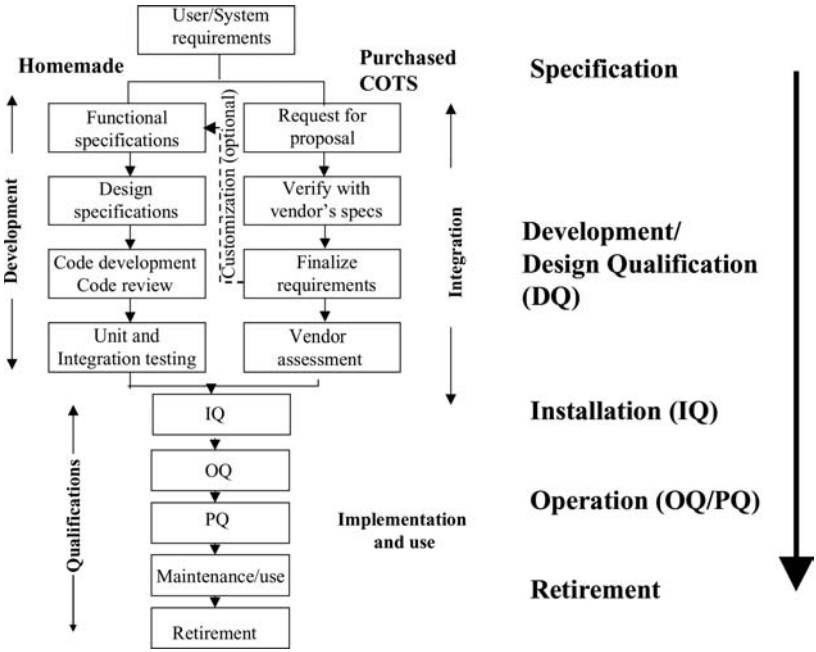


Figure 1 System integration combined with system development. *Abbreviation*: COTS, commercial off-the-shelf system. *Source*: Ref. 74.

Programmers develop functional specifications, design specifications, and the code and perform testing in all development phases under supervision of the quality assurance. The development and qualification phases are described in detail in Reference 73.

Commercial systems follow the system integration lifecycle on the right. Either the SRS or a special Request for Proposal (RFP) is sent to one or more vendors (see right side of the diagram). Vendors either respond to each requirement or with a set of functional specifications of a system that is most suitable for the user's requirements. Users compare the vendor's responses with their own requirements. If none of the vendors meet all user requirements, the requirements may be adjusted to the best fit or additional software is written to fulfill the user requirements following the development cycle on the left side of the diagram. The vendor that best meets the user's technical and business requirements is selected and qualified.

TESTING

Testing typically is the most time consuming step of computer systems validation. Because of problems mentioned above, there is more uncertainty for

testing software and computer systems than for testing equipment hardware. The basic questions are as follows:

- How much testing is enough?
- Should all functions be tested?
- Tests have been performed during and at the end of development; should all these tests be repeated?
- How to perform the tests?
- How to document the test?
- If I have multiple computers with the same configurations, either at one site, or at multiple sites, should I repeat all tests for all systems?

Too much testing can become quite expensive, and insufficient testing can be a problem during an audit and when undiscovered failures occur during ongoing use. For example, the author has seen test protocols of 200 and more pages that users of an off-the-shelf commercial computerized chromatographic system developed over several weeks. Each software function, such as switching the integrator on and off, has been verified as part of an OQ procedure. This is not necessary if the tests have been done and documented at the vendor's site.

Risk-based validation is the answer to most of the questions. The type and extent of testing required for the qualification of software and computer systems depends very much on the type and complexity of the software and on the impact of records generated by the system on product quality, patient safety, and overall business. The concept of risk-based validation has been discussed in chapter four of this book and will not be further evaluated in this chapter.

The GAMP good practices guide (7) on the validation of laboratory computer systems has segmented laboratory systems in seven categories with different complexities. The guide gives recommendations for procedures and validation deliverables for each category. The first three categories are instruments with digital control but do not include computers for storage of data. OQ of these instruments is covered in chapter eight of this book.

Related to complexity and application of systems with computers, we can differentiate between three different situations leading into further discussions in this chapter:

- Vendor-supplied software and computer hardware is an integral part of an analysis system, for example, a computerized spectrometric system where the computer is used for instrument control, data acquisition, and data evaluation. Testing done by the vendor can be leveraged for user testing. Testing of software functions related to the application can be done while processing reference samples.

- Several computer systems are interconnected to each other and may also be interfaced to analytical systems. Examples are client/server-based chromatographic data systems and laboratory information management systems (LIMS). Before the application is installed and validated, the infrastructure supporting the application should be qualified.
- Software has been developed in the user's laboratory as an add-on to a vendor-supplied software package, e.g., a macro or a stand-alone software package. Excel spreadsheet applications with custom calculations and VBA scripts also fall in this category. This requires most intensive testing of each function.

Indeed, in practice, many computer systems found in analytical laboratories are combinations of categories 1, 2, and 3. The validation requirements for each category will be discussed separately. If combinations of the categories are used, the validation activities can also be combined. Testing is very different among the categories, but the basic procedure is the same for all three categories.

- Define the functions and criticality for each function.
- Develop test cases for critical functions, and define expected results and acceptance criteria in a test plan.
- Approve test plan before the tests start.
- Execute the tests.
- Compare the actual test results with the expected results and acceptance criteria.
- Approve and document everything.

For testing software, test protocols should be developed that include a cover page with information about test environments, instrument configuration, and software revision. The templates should include entry fields for the test person, the function to be tested, the rationale for testing, expected results, and observations of actual results made during testing. Simple pass/fail indications are insufficient. Figure 2 shows an example for a test template.

COMPUTERIZED ANALYSES SYSTEMS

Correct functioning of software loaded on a computer system should be checked in the user's laboratory under typical operating conditions. During

Test ID:	**Test System ID**:
Test Objectives:	
Reference to Requirement Specification Procedures:	
Prerequisites:	

Test Procedure

Step	Test Procedure	Expected Result	Required Documents	Observation	Pass/fail Initials
1					☐ passed ☐ failed Initials ____
2					☐ passed ☐ failed Initials ____

Tester: I confirm that I have all tests executed as described

Name: _____ Signature: _____ Date: _____

Test passed: yes ☐ no ☐ Comment: _____

Reviewer: I confirm that I have reviewed test documentation

Name: _____ Signature: _____ Date: _____

Comment:

_____

Figure 2 Test template for computer system validation. *Source*: Ref. 103.

the equipment hardware test, as described in the previous section, many software functions are executed and can be tested.

- Instrument control
- Data acquisition

- Peak integration
- Quantitation
- File storage
- File retrieval
- Printing
- Settings of special configuration

Therefore, with the successful completion of hardware tests, it can also be assumed that the chromatography-related software operates as intended. In addition, critical software functions not directly related to chromatographic performance tests should be formally tested and results documented. They include the following:

- Access control
- Electronic Audit trail
- Backup and retrieval
- Disaster recovery
- Important error messages and diagnostic functions
- Electronic signatures, if part of the requirement specifications

Another possibility is to run a well-characterized test sample under normal and stress conditions (e.g., run multiple systems in parallel and compare the newly calculated results with results from previous runs).

There are two situations where software verification, independent of the equipment hardware, may be necessary:

1. Not all critical software functions are executed during the hardware verification (e.g., spectral evaluation).
2. A verification of the software functions is done without a need for equipment testing. This is the case after a change on the computer system, for example, if a new version of the operating system has been installed or if new hardware, such as CD-ROMs, internal memory (RAM), or a hard disk, has been installed on the computer system.

Most software functions of a chromatographic computerized system can also be tested by using well-characterized data files without injecting a test sample. The advantage is that less time is required for the test. The concept has been described in great detail in Reference 69 and is summarized in Table 1. The procedure is very useful after updating the computer system, for example, after adding more internal memory or when changing to a new operating system. The test procedure is very generic and can also be used to test and verify the correct functions of other software packages.

Table 1 Qualification Process of Chromatographic Computer Systems using Reference Data Files

Generation of Master Data
1. Generate one or more master chromatograms (the chromatograms should reflect typical samples).
2. If the method uses spectral data, generate master spectra with spectral libraries.
3. Develop integration method, calibration method and procedure for spectral evaluation, for example, peak purity, and/or identity checks.
4. Generate and print out master result(s).
5. Save master chromatograms, master method, and results on paper and store them electronically as data files.
Verification
1. Select data file with master chromatogram (and spectra).
2. Select file with master method for data processing (integration, quantitation, spectral evaluation, etc.).
3. Run test manually or automatically. Automation is preferred because it is faster and has less chance for errors to occur.
4. Compare test results with master data. Again, this can be done automatically if such software is built into the system.
5. Print and archive results.

Source: Ref. 73.

Well-characterized test chromatograms and spectra derived from standards or real samples are stored on disk as a master file. Chromatograms and spectra may be supplied by the vendor as part of the software package. The vendor-supplied chromatograms and spectra are only useful if they reflect the user's way of working; otherwise, test chromatograms and spectra should be recorded by the user. This *master data file* passes through normal data evaluation from spectral evaluation and integration to report generation. Results are stored on the hard disk. Exactly the same results should always be obtained when using the same data file and method for testing purposes. If the chromatographic software is used for different methods, the test should be for different methods. For example, one test can be a setup assay and another can be for impurity tests.

Preferably, tests and documentation of results should be done automatically, always using the same set of test files. In this way, users are encouraged to perform the tests more frequently, and user-specific errors are eliminated. In some cases, vendors provide test files and automated test routines for verification of a computer system's performance in the user's laboratory. Needless

Table 2 Steps to Build a Qualified Network Infrastructure

- Specify network requirements. Specifications should include: network devices, software, computer hardware, computer peripherals cables. Specifications are based on anticipated current and future use of the network.
- Develop a network infrastructure plan.
- Design network infrastructure and drawings.
- Select equipment and vendors for computers, NOS, network devices, etc.
- Order equipment: computer hardware, software (OS, NOS), network devices, peripherals.
- Install all hardware devices according to design drawings and vendor documentation.
- Perform self-diagnostics, document hardware installation, and settings (this completes the IQ part).
- Document this as network baseline.
- Make a backup of installed software and network configurations. Whatever happens, it should be possible to return to this point.
- Test communication between networked computers and peripherals, and access control including remote access control.
- Develop and implement rigorous configuration management and change control procedure for all your network hardware and software. This also should include updates of system drawings if there are any changes.
- Before applying any system changes to a production environment they should be verified in a test environment to ensure that one does not impact the intended functionality of the system.
- Monitor ongoing network traffic using a network health monitoring software for this.

Abbreviations: IQ, installation qualification; NOS, network operating system; OS, operating system. *Source*: Ref. 73.

to say, the correct functioning of this software should also be verified. This can easily be done by changing the method or data file and rerunning the test. The report should indicate an error. If automated verification software is not available, the execution of the tests, the verification of actual results with prerecorded results, and documentation can be done manually.

Successful execution of this procedure ensures that

- the actual version of the application software works correctly for the tested functions,
- executed program and data files are loaded correctly on the hard disk,
- the actual computer hardware is compatible with the software, and
- the actual version of the operating system and user interface software is compatible with the application software.

NETWORKED SYSTEMS

Before applications running on a network are validated, the network infrastructure should be qualified.

After the network infrastructure is qualified, the application is installed and validated using common computer validation practices. Testing should include access control to the network and tasks and network transactions under normal and high load. Data sets should be developed and input on 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

- the chromatographic data system, and
- the server after storage and retrieval of the files.

The results should be compared, either manually or automatically.

EXISTING SYSTEMS AND SYSTEMS WITHOUT EVIDENCE OF VENDOR VALIDATION

Existing computer systems in laboratories requires retrospective evaluation and qualification if their initial validation was not formally documented. Typical questions are as follows:

- Do I have to validate existing systems?
- Should the same validation criteria and procedures be applied for existing systems as for new systems?
- What if I cannot get any documented evidence from the vendor about validation during development?
- What type of testing do I have to do?
- How can I use the test data that I have collected in the past?

There is no doubt that existing systems should be validated if data generated on the system are critical for product quality and consumer safety; however, it is difficult to use the same validation criteria for an older computer system as those used for a new one. The software might not have been developed in accordance with the most recent product life-cycle guidelines, and full documentation may not have been archived.

Fortunately, existing computer systems have an advantage not shared by new systems—the experience gained over time. The validation process can take advantage of this wealth of historical experience by reviewing the quality of analytical results obtained from computerized systems. Such a review may provide sufficient evidence that the system has done and is still

doing what it is supposed to do. In this case, retrospective evaluation and validation are just a matter of documenting what already has been done in the past.

The validation of existing systems takes time, and it is quite obvious that not all existing systems can be validated at one particular time; it may not even be necessary to validate all systems in a laboratory. Therefore, the validation process should follow a multi-step plan:

1. Identify all analytical systems with computers in a laboratory.
2. Identify those systems that need to be validated.
3. Develop a validation schedule for those systems that need to be validated.
4. Implement the schedule.

Before a decision is made to qualify an existing system retrospectively, serious thought should be given whether to purchase a new system or to update the current one. Important criteria to consider are the anticipated costs of a retrospective validation versus purchasing and validating a new system and an estimation on how successful the retrospective validation will be. The latter can be estimated by looking at the history of the computer system and checking for regular maintenance, calibrations, and performance checks and trouble-free operation over a long period.

Once the decision has been made to qualify the system, a plan and documentation should be prepared. Ideally, the same documentation should be available for existing systems, as described in the previous chapter, as for new systems; every attempt should be made to acquire this information.

The qualification protocol for an existing system should include a list of missing documentation usually required for validation. The protocol should also provide an explanation as to why the documentation is missing. In many cases, the qualification may have been performed, but the relevant data was not documented. In other cases, the data may have been retained, but proper authorization signatures were not obtained. The validation plan should also contain a contingency plan that describes what should be done if the previously generated data are deemed to be incorrect (e.g., who should be notified).

After evaluation and qualification, the following documentation should be available:

- The qualification plan and protocol
- A description of the system hardware and software
- Historical logs of hardware with system failure reports, maintenance logs and records, as well as calibration records

- Test data demonstrating that the system does what it purports to do (this can be system suitability test results or well-documented QC charts)
- Procedures and schedules for preventive maintenance and ongoing performance testing (e.g., regular system suitability tests or the analysis of QC samples)
- A plan for error recording, reporting, and remedial action

A similar qualification procedure is recommended for new systems if the vendor will not, or cannot, provide evidence of development validation. However, this qualification requires more intensive testing because the system has provided no previous data. If the analysts are familiar with the technique, and well-defined reference samples are available, testing the system as a whole using the reference samples with the anticipated operating ranges can be adequate. Users should compare the results with results obtained from other instruments currently in use.

If the analysts have little or no experience with the analysis technique or if no reference data are available, use the modular test approach to examine each system and software program module by module, checking for correct instrument control, peak integration, compound quantitation, and data storage and retrieval.

Tests should be included that check the system's error-handling capabilities. The system should recognize and display any wrong entry, such as flow rates greater or smaller than the operational range. Another simple test could check how the program responds when alphabetic data are input to entry fields that are designed to accept numeric data. The tests should also check system boundary conditions. To test these conditions, input data that are slightly greater or less than the operational limits. For example, if the operational limit of a gas chromatograph's oven is 400°C, try entering values of 399°C and 401°C.

USER-CONTRIBUTED SOFTWARE (E.G., MACROS)

Application software developed by the user should be fully validated and documented by the user. Such software may be a stand-alone software package (e.g., for statistical data evaluation), or it may be an extension to purchased standard software (e.g., a macro or VBA Script to enhance functionality, e.g., for Excel spreadsheet). The development and validation of such software should follow a documented procedure, and the source code should be available. The effort involved in validation depends very much on the size and complexity of the program. The development of large programs should follow the software development life cycle and can take several weeks or months. Validation can take several weeks, and the documentation will be extensive.

On the other hand, the validation of smaller programs can be done in a few hours, and the documentation may be only a few pages. The development, validation, and documentation of such small programs requires, at minimum, the following steps:

1. Describe the problem, how the problem is solved currently, and how the newly developed program will solve it.
2. Identify responsibilities for development, test, and approvals.
3. Describe the task and the system requirements (hardware, system software, standard software).
4. Describe the program in terms of the functions it will perform.
5. Document formulas and algorithms used within the code.
6. Write and document the code in such a way that it can be understood by other people whose knowledge and experience are similar to the programmer's. Print the code.
7. Develop test cases and data sets with known inputs and outputs. Include test cases with normal data across the operating range, some at the boundary and some unusual cases with incorrect inputs. The results should be calculated by the new program and also by using alternative methods. The development of an automated test procedure that can be executed as often as possible is recommended. Test procedures and results should be documented, reviewed, and signed off.
8. Develop user documentation with information on how to install, test, and operate the program.
9. Describe and implement procedures for data backup and security routines for limited access to authorized people.
10. Develop a procedure to authorize, test, document, and approve any changes to the software and documentation.

For combined systems, vendor-updated software revisions may be critical, especially if the updated version supplied by the vendor will have an effect on the interface between the vendor's and the user's software (e.g., if the meaning of a macro command has been changed). The user should obtain information from the vendor on how the updated version may affect the interface. The user should also test his or her software after it has been integrated into the vendor's updated standard software. More details about SOPs for developing and validating simple, as well as complex, application software developed in the user's laboratory are found elsewhere (73).

VALIDATION FOR 21 CFR PART 11 COMPLIANCE

The FDA's regulation on electronic records and signatures, 21 CFR Part 11 (42), requires that computer systems used to acquire, evaluate, and transmit

and store electronic records should be validated. This is nothing new and processes and steps to validate such systems should follow steps described earlier on in this chapter. Specific functions to be tested as required by Part 11 are as follows:

- Limited authorized access to data and systems
- Computer generated audit trail
- Binding signatures to records
- Accurate copies of electronic records
- Ready retrieval for processing of data

Required steps to achieve validation compliance are not different from other validation steps. They are described in detail in Reference 99. Key points are listed below:

- Specify requirements and include them in your user requirement specifications document. Information on the requirements can be obtained from the regulation itself and from the Part 11 industry guidance Scope and Applications (64).
- Develop test procedures to verify that the functions meet the requirements.

Recommended test procedures include:

1. *Limited and authorized system access.* This can be achieved by entering correct and incorrect password combination and verify if the system behaves as intended.
2. *Limited access to selected tasks and permissions.* This can be achieved by trying to get access to tasks as permitted by the administrator and verify the system behaves as specified.
3. *Computer-generated audit trail.* Perform actions that should go into the e-audit trail according to specifications. Record the actions manually compare and compare the recordings with computer generated audit trail
4. *Accurate and complete copies.* Calculate results from raw data using a defined set of evaluation parameters (e.g., chromatographic integrator events, calibration tables, etc.). Save raw data, final results, and evaluation parameters on a storage device. Switch off the computer. Switch it on again and perform the same tasks as before using data stored on the storage device. Results should the same as for the original evaluation.

5. *Binding signatures with records.* Sign a data file electronically. Check the system design and verify that there is a clear link between the electronic signature and the data file. For example, the link should include the printed name or a clear reference to the person who signed, the date and time, and the meaning of the signature.

IMPLEMENTATION AND DOCUMENTATION

Some important points should be considered for the implementation of OQ of software and computer systems:

1. For complex systems, a validation team should be formed consisting of analysis experts from the laboratories affected, computer experts from IT departments, and validation experts.
2. An overall validation plan should be developed that describes the purpose of the system, including subsystems, responsible persons, test philosophy, and a schedule for testing. OQ should be part of this plan.
3. The intended use and functions of the system and all subsystems should be defined. For subsystems and core functions of the network, the vendor should provide a list with detailed functional specifications. From these specifications, the user can derive the functions the systems will employ in the user's laboratory.
4. For networked systems, test cases should be developed for each subsystem, and each subsystem should be validated.
5. A test plan with test cases and acceptance criteria should be developed and approved before the tests start.
6. All or at least some tests should be done under high data flow.
7. When there is a change to the system, the validation team should evaluate the possible impact of the change on other parts of the system. Based on this evaluation, a test plan should be developed that executes either all or part of the tests as specified in step 3.

At the end of OQ, documentation should be available or developed that includes a validation protocol with

- the description, intended use, and unique identification of equipment;
- functional specifications;

- test protocols to include test items, acceptance criteria, actual test results, date and time when tests have been performed, and a list of the names of people who performed the tests as well as signatures; and
- a summary of results and a statement on the validation status.

Summary Recommendations

1. For complex systems, establish a validation team and develop a validation project plan.
2. Define intended functions and their criticality.
3. Define tests and acceptance criteria.
4. For commercial systems with validation documents from the vendor, test critical functions and functions that can be impacted by the environment. Otherwise rely on vendor testing.
5. Execute and document tests.
6. For networked systems, first qualify the network, then install and validate the application.
7. Develop and implement a procedure for software developed in the user's laboratory.
8. For existing systems, evaluate and qualify the system based on past experience.
9. If there is no evidence of sufficient testing, functions should be formally tested.

11

Validation of Analytical Methods

What Is Discussed in this Chapter?

1. How to develop and implement a strategy for method validation
2. The parameters that should be validated
3. Difference between USP and ICH procedures
4. How to verify standard methods
5. How to validate non-routine methods
6. How to implement validated methods in routine use
7. How to transfer validated methods
8. When and how a method should be revalidated

INTRODUCTION

Method validation is the process used to confirm that the analytical procedure employed for a specific test is suitable for its intended use. Results from method validation can be used to judge the quality, reliability, and consistency of analytical results; it is an integral part of any good analytical practice.

Analytical methods need to be validated or revalidated

- before their introduction into routine use;
- whenever the conditions change for which the method has been validated (e.g., an instrument with different characteristics or samples with a different matrix); and
- whenever the method is changed and the change is outside the original scope of the method.

Method validation has received considerable attention in the literature and from industrial committees and regulatory agencies.

The U.S. FDA CGMP (1) request in section 211.165 (e) methods to be validated:

> *The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm shall be established and documented. Such validation and documentation may be accomplished in accordance with Sec. 211.194(a).*

These requirements include a statement of each method used in testing the sample to meet proper standards of accuracy and reliability, as applied to the tested product. The U.S. FDA has also proposed industry guidance for Analytical Procedures and Methods Validation (2).

ISO/IEC 17025 includes a chapter on the validation of methods (53) with a list of nine validation parameters. The ICH (4) has developed a consensus text on the validation of analytical procedures. The document includes definitions for eight validation characteristics. ICH also developed guidelines with detailed methodology (5).

The U.S. EPA prepared guidelines for methods development and validation for the Resource Conservation and Recovery Act (RCRA) (8). The AOAC, the EPA, and other scientific organizations provide methods that are validated through multi-laboratory studies.

The USP has published specific guidelines for method validation for compound evaluation (28). USP defines eight steps for validation:

1. Accuracy
2. Precision
3. Specificity
4. Limit of detection
5. Limit of quantitation
6. Linearity and range
7. Ruggedness
8. Robustness

The FDA has also published guidelines for the validation of bioanalytical methods (3). The most comprehensive document is the conference report of the 1990 Washington conference: *Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies,* which was sponsored by, among others, the American Association of Pharmaceutical Scientists (AAPS), the AOAC and the U.S. FDA (75). The report presents guiding principles for validating studies of both human and animal subjects. The report has also been used as a basis for the FDA industry guidance document (3).

Representatives of the pharmaceutical and chemical industry have published papers on the validation of analytical methods. Hokanson (76,77)

applied the life-cycle approach, developed for computerized systems, to the validation and revalidation of methods. Green (78) gave a practical guide for analytical method validation, with a description of a set of minimum requirements for a method. Renger and his colleagues (79) described the validation of a specific analytical procedure for the analysis of theophylline in a tablet using high-performance thin layer chromatography (HPTLC). The validation procedure in this particular article is based on requirements for EU multi-state registration.

Wegscheider (80) has published procedures for method validation with a special focus on calibration, recovery experiments, method comparison, and investigation of ruggedness. Seno et al. (81) have described how analytical methods are validated in a Japanese QC laboratory. The AOAC (9) has developed a Peer-Verified Methods validation program with detailed guidelines on exactly which parameters should be validated. Winslow and Meyer (82) recommend the definition and application of a master plan for validating analytical methods. J. Breaux and colleagues have published a study on analytical methods development and validation (83). The key point is to develop methods for easy validation and revalidation. S.O. Krause published a guide for analytical method transfer, comparability, maintenance, and acceptance criteria for the testing of biopharmaceuticals (84).

This chapter gives a review and a strategy for the validation of analytical methods for both methods developed in-house as well as standard methods, and a recommendation on the documentation that should be produced during, and on completion of, method validation. It also describes what is important when transferring a method.

STRATEGY FOR THE VALIDATION OF METHODS

The validity of a specific method should be demonstrated in laboratory experiments using samples or standards that are similar to unknown samples analyzed routinely. 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 Table 1. This proposed procedure assumes that the instrument has been selected and the method has been developed. It 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.

Successful acceptance of the validation parameters and performance criteria, by all parties involved, requires the cooperative efforts of several departments, including analytical development, QC, regulatory affairs, and the individuals requiring the analytical data. The operating procedure or the Validation Master Plan (VMP) should clearly define the roles and responsibilities of each department involved in the validation of analytical methods.

Table 1 Steps in Method Validation

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

Abbreviation: SOP, standard operating procedure.

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

- 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 on one side or around the globe?
- What skills do the anticipated users of the method have?

Table 2 Validation Parameters for Different Analysis Tasks

	Major compounds	**Major compounds and traces**	**Traces**	**Traces**
	Quantitative	Quantitative	Qualitative	Quantitative
Limit of detection	No	No	Yes	No
Limit of quantitation	No	Yes	No	Yes
Linearity	Yes	Yes	No	Yes
Range	Yes	Yes	No	No
Precision	Yes	Yes	No	Yes
Accuracy	Yes	Yes	No	Yes
Specificity	Yes	Yes	Yes	Yes
Ruggedness	Yes	Yes	No	Yes

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 analytical chemist performing the validation and the lab or individual applying the method and users of the data to be generated by the method. Table 2 gives examples of which parameters might be tested for a particular analysis task.

The scope of the method should also include the different types of equipment and the locations where the method will be run. For example, if the method is to be run on a specific instrument in a specific laboratory, there is no need to use instruments from other vendors or to include other laboratories in the validation experiments. In this way, the experiments can be limited to what is really necessary.

The validation experiments should be carried out by an experienced analyst to avoid errors due to inexperience. The analyst should be very well versed in the technique and operation of the instrument. Before an instrument is used to validate a method, its performance specifications should be verified using generic chemical standards. Satisfactory results for a method can be obtained only with equipment that is performing well. Special attention should be paid to those equipment characteristics that are critical for the method. For example, if detection limit is critical for a specific method, the instrument's specification for baseline noise and, for certain detectors, the response to specified compounds should be verified.

Any chemicals used to determine critical validation parameters, such as reagents and reference standards, should be

1. available in sufficient quantities,
2. accurately identified,
3. sufficiently stable, and
4. checked for exact composition and purity.

Any other materials and consumables, for example, chromatographic columns, should be new and be qualified to meet the column's performance criteria. This ensures that one set of consumables can be used for most experiments and avoids unpleasant surprises during method validation.

Operators should be sufficiently familiar with the technique and equipment. This will allow them to identify and diagnose unforeseen problems more easily and to run the entire process more efficiently.

If there is little or no information on the method's performance characteristics, it is recommended to prove the suitability of the method for its intended use in initial experiments. These studies should include the approximate precision, working range, and detection limits. If the preliminary validation data appear to be inappropriate, the method itself, the equipment, the analysis technique, or the acceptance limits should be changed. Method development and validation are, therefore, an iterative process. For example, in liquid chromatography, selectivity is achieved through the selection of mobile phase composition. For quantitative measurements, the resolution factor between two peaks should be 2.5 or higher. If this value is not achieved, the mobile phase composition needs further optimization. The influence of operating parameters on the performance of the method should be assessed at this stage if this was not done during development and optimization of the method.

There are no official guidelines on the correct sequence of validation experiments, and the optimal sequence may depend on the method itself. Based on the author's experience, for a liquid chromatographic method, the following sequence has proven to be useful:

1. Selectivity of standards (optimizing separation and detection of standard mixtures if selectivity is insufficient)
2. Linearity, limit of quantitation, limit of detection, range
3. Repeatability (short-term precision) of retention times and peak areas
4. Intermediate precision
5. Selectivity with real samples
6. Trueness/accuracy at different concentrations
7. Ruggedness (interlaboratory studies)

The more time-consuming experiments, such as accuracy and ruggedness, are included toward the end. Some of the parameters, as listed under (2) to (6), can be measured in combined experiments. For example, when the precision of peak areas is measured over the full concentration range, the data can be used to validate the linearity.

During method validation, the parameters, acceptance limits, and frequency of ongoing system suitability tests or QC checks should be defined. Criteria should be defined to indicate when the method and system are beyond statistical control. The aim is to optimize these experiments so that, with a minimum number of control analyses, the method and the complete analytical system will provide long-term results to meet the objectives defined in the scope of the method.

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

- Objective and scope of the method (applicability, type).
- Summary of methodology.
- Type of compounds and matrix.
- All chemicals, reagents, reference standards, QC 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 the method development lab to routine analysis.
- Method parameters.
- Critical parameters taken from robustness testing.
- Listing of equipment and its functional and performance requirements, e.g., cell dimensions, baseline noise, and column temperature range. For complex equipment, a picture or schematic diagram 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 QC in routine analyses, e.g., system suitability tests.
- Representative plots, e.g., chromatograms, spectra, and calibration curves.
- Method acceptance limit performance data.
- The expected uncertainty of measurement results.
- Criteria for revalidation.
- The person(s) who developed and validated the method.

- References (if any).
- Summary and conclusions.
- Approval with names, titles, date, and signature of those responsible for the review and approval of the analytical test procedure.

VERIFICATION OF STANDARD METHODS

A laboratory applying a specific method should have documented evidence that the method has been appropriately validated. This holds for methods developed in-house, as well as for standard methods, for example, those developed by organizations such as the EPA, American Society for Testing and Materials (ASTM), ISO, or the USP.

A number of questions usually arise about the validation of standard methods: Firstly, should these methods be revalidated in the user's laboratory and, if so, should method revalidation cover all experiments, as performed during initial validation? Secondly, which documentation should be available or developed in-house for standard methods? Official guidelines and regulations are not explicit about validating standard methods. Only CITAC/EURACHEM guide (31) includes a short paragraph that reads as follows:

> *The validation of standard or collaboratively tested methods should not be taken for granted, no matter how impeccable the method's pedigree – the laboratory should satisfy itself that the degree of validation of a particular method is adequate for the required purpose, and that the laboratory is itself able to match any stated performance data.*

There are two important requirements in this excerpt:

1. The standard's method validation data are adequate and sufficient to meet the laboratory's method requirements.
2. The laboratory must be able to match the performance data as described in the standard.

Further advice comes from FDA's 21 CFR 194 section (a)2:

> *If the method employed is in the current revision of the United States Pharmacopeia, National Formulary, Association of Official Analytical Chemists, or in other recognized standard references, or is detailed*

in an approved new drug application and the referenced method is not modified, a statement indicating the method and reference will suffice. The suitability of all testing methods used shall be verified under actual conditions of use.

This section elaborates on what these statements mean in practice, and it gives a strategy for validating standard methods. Like the validation of methods developed in-house, the evaluation and verification of standard methods should also follow a documented process that is usually the validation plan. Results should be documented in the validation protocol. Both documents will be the major source for the validation report.

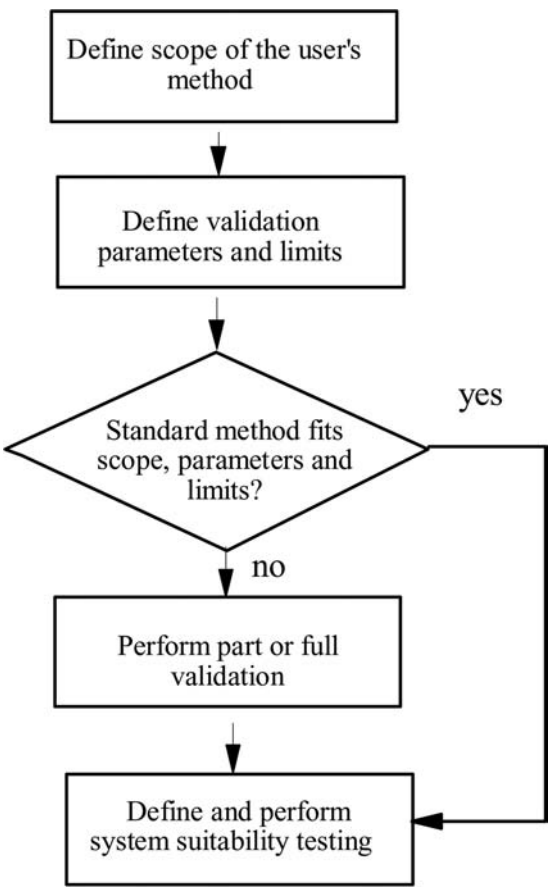


Figure 1 Workflow for evaluation and validation of standard methods.

An example of a step-by-step plan for the evaluation and validation of standard methods is shown as a flow diagram in Figure 1. As a first step, the scope of the method, as applied in the user's laboratory, should be defined. This should be done independently of what is written in the standard method and should include information such as

- the type of compounds to be analyzed,
- matrices,
- the type of information required (qualitative or quantitative),
- detection and quantitation limits,
- range,
- precision and accuracy as specified by the client of the analytical data, and
- the type of equipment—its location and environmental conditions.

As a second step, the method's performance requirements should be defined in considerable detail, again, irrespective of what has been validated in the standard method. General guidelines on validation criteria for different measurement objectives and procedures for their evaluation are discussed later in this chapter.

The results of these steps lead to the experiments that are required for adequate method validation and to the minimal acceptance criteria necessary to prove that the method is suitable for its intended use. Third, required experiments and expected results should be compared with what is written in the standard method.

In particular, the standard method should be checked for the following items:

1. Have the reported validation results been obtained from the complete procedure or from just a part of it? Sometimes the validation data from the published method have been obtained from the chromatographic analysis but have not included sample preparation steps. The diagram in Figure 2 can be used for this check. A complete validation of the analytical procedure should include the entire process from sampling, sample preparation, analysis, calibration, and data evaluation to reporting.
2. Has the same matrix been used?
3. Did the validation experiments cover the complete concentration range as intended for the method in the user's laboratory? If so, has the method's performance been checked at the different concentration ranges?

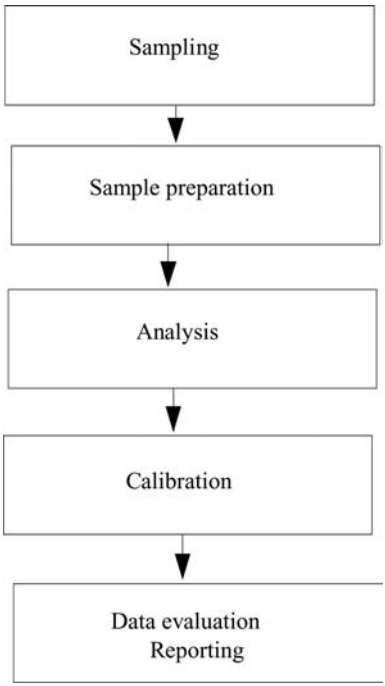


Figure 2 Steps for validating complete analytical procedures. Standard methods should be checked if all steps are included in the validation data.

4. Has the same equipment (brand, model) been used as available in the user's laboratory, and, if not, was the scope of standard method regarding this item broad enough to include the user's equipment? This question is very important for a gradient HPLC analysis, where the HPLC's delay volume can significantly influence the method's selectivity.
5. Have performance characteristics, e.g., the limit of quantitation, been checked in compliance with the most recent guidelines, as required for the user's laboratory [e.g., the ICH guideline (5) for pharmaceutical laboratories]? If not, does the test procedure have equivalency to the guideline?

If the scope, the validation parameters, or the validation results do not meet the user's requirements, adequate validation experiments should be

defined, developed, and carried out. The extent of these experiments depends on the overlap of the user requirements with the scope and results, as described in the standard method. If there is no overlap, a complete validation should be carried out. In the case of a complete overlap, validation experiments may not be necessary.

If method validation experiments are unnecessary, the user should prove the suitability of the method in his or her laboratory. This evidence should confirm that the user's equipment, the people, the reagents, and the environment are qualified to perform the analysis. The experiments may be an extract of the full method validation and should focus on the critical items of the method. Guidelines for these tests should have been developed during method development. If not, they should be developed and carried out at this stage. Typical experiments may include precision of amounts and limits of quantitation.

The validation report should include a reference to the standard method.

VALIDATION OF NON-ROUTINE METHODS

Frequently, a specific method is used for only a few sample analyses. The question should be raised as to whether this method also needs to be validated using the same criteria as recommended for routine analysis. In this case, the validation may take much more time than the sample analysis and may be considered inefficient, because the cost per sample will increase significantly. The answer is quite simple: Any analysis is worthwhile only if the data are sufficiently accurate; otherwise, sample analysis is pointless. The suitability of an analysis method for its intended use is a prerequisite to obtaining accurate data; therefore, only validated methods should be used to acquire meaningful data. However, depending on the situation, the validation efforts can be reduced for non-routine methods. The CITAC/EURACHEM guide (31) includes a chapter on how to treat non-routine methods. The recommendation is to reduce the validation cost by using generic methods, for example, methods that are broadly applicable. A generic method could, for example, be based on capillary gas chromatography or on reversed-phase gradient HPLC. With little or no modification, the method can be applied to a large number of samples. The performance parameters should have been validated on typical samples characterized by sample matrix, compound types, and concentration range.

If, for example, a new compound with a similar structure in the same matrix is to be analyzed, the validation will require only a few key experiments. The documentation of such generic methods should be designed to easily accommodate small changes relating to individual steps, such as sample preparation, sample analysis, or data evaluation.

The method's operating procedure should define the checks that need to be carried out for a novel analyte in order to establish that the analysis is valid. Detailed documentation of all experimental parameters is important to ensure that the work can be repeated in precisely the same manner at any later date.

QUALITY CONTROL PLAN

For any method that will be used for routine analysis, a QC plan should be developed. This plan should ensure that the method, together with the equipment, delivers consistently accurate results. The plan may include recommendations for the following:

1. Selection, handling, and testing of QC standards
2. Type and frequency of equipment checks and calibrations (for example, should the wavelength accuracy and the baseline noise of an HPLC UV detector be checked after each sample analysis, or on a daily or weekly basis?)
3. Type and frequency of system suitability testing (for example, at which point during the sequence system should suitability standards be analyzed?)
4. Type and frequency of QC samples (for example, should a QC sample be analyzed after 1, 5, 20, or 50 unknown samples, and should there be single or duplicate QC sample analysis, or should this be run at one or several concentrations?)
5. Acceptance criteria for equipment checks, system suitability tests and QC sample analysis
6. Action plan in case criteria 2, 3, and/or 4 are not met

IMPLEMENTATION TO ROUTINE ANALYSIS

In many cases, methods are developed and validated in service laboratories that are specialized in this task. When the method is transferred to the routine analytical laboratory, care should be taken that the method and its critical parameters are well understood by the workers in the departments who apply the method. A detailed validation protocol, a documented procedure for method implementation, and good communication between the development and operation departments are equally important. If the method is used by a number of departments, it is recommended to verify method validation parameters and to test the applicability and usability of the method in a couple of these departments before it is distributed to other departments. In this way, problems can be identified and corrected before the method is distributed to

a larger audience. If the method is intended to be used by just one or two departments, an analyst from the development department should assist the users of the method during initial operation. Users of the method should be encouraged to give constant feedback on the applicability and usability of the method to the development department. The latter should correct problems if any arise.

TRANSFERRING VALIDATED ROUTINE METHODS

Validated routine methods are transferred between laboratories at the same or different sites when contract laboratories offer services for routine analysis in different areas or when products are manufactured in different areas. When validated routine methods are transferred between laboratories and sites, their validated state should be maintained to ensure the same reliable results in the receiving laboratory. This means the competence of the receiving laboratory to use the method should be demonstrated through tests, for example, repeating critical method validation experiments and running samples in parallel in the transferring and receiving laboratories. The transfer should be controlled by a procedure. The recommended steps are

- Designate a project owner
- Develop a transfer plan
- Define transfer tests and acceptance criteria (validation experiments, sample
  analysis: sample type, number of replicates)
- Describe rationale for tests
- Train receiving lab operators in transferring lab on equipment, method, critical parameters, and troubleshooting
- Repeat two critical method validation tests in routine lab
- Analyze at least three samples in transferring and receiving lab
- Document transfer results

REVALIDATION

Most likely some method parameters have to be changed or adjusted during the life of the method if the method performance criteria fall outside their acceptance criteria. The question is whether such change requires revalidation. In order to clarify this question up front, operating ranges should be defined for each method, either based on experience with similar methods or else investigated during method development. 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

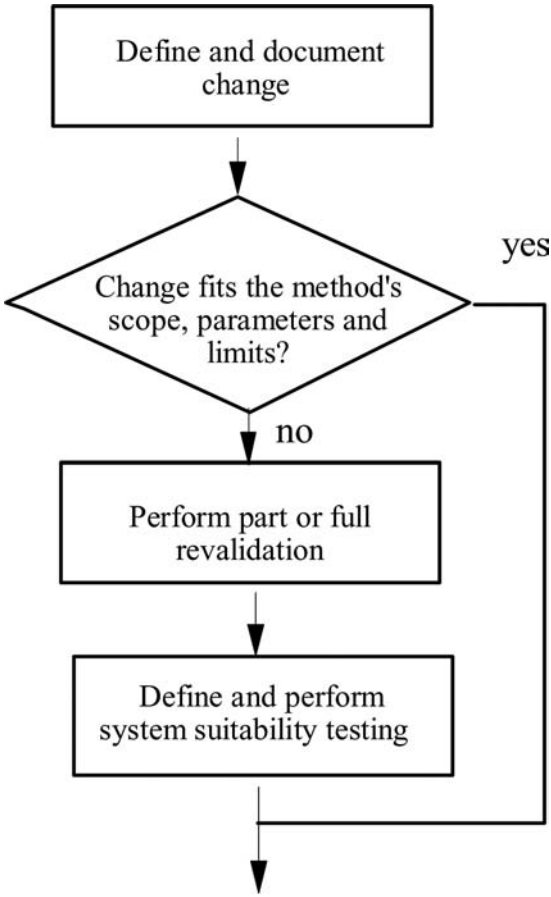


Figure 3 Flow diagram for revalidation.

to decide when a method should be revalidated. A revalidation is necessary whenever a method is changed and the new parameter lies outside the operating range. If, for example, the operating range of the column temperature has been specified to be between 30°C and 40°C, the method should be revalidated if, for whatever reason, the new operating parameter is 41°C.

Revalidation is also required if the scope of the method has been changed or extended, for example, if the sample matrix changes or if operating conditions change. Furthermore, revalidation is necessary if the intention is to use instruments with different characteristics and these new characteristics have not been covered by the initial validation. For example, an HPLC method may have been developed and validated on a pump with a delay volume of 5 mL, but the new pump has a delay volume of only 0.5 mL.

Part or full revalidation may also be considered if system suitability tests, or the results of QC sample analysis, lie outside preset acceptance criteria and where the source of the error cannot be traced back to the instruments or any other cause.

Whenever there is a change that may require part or full revalidation, the change should follow a documented change control system. A flow diagram of such a process is documented in Figure 3. The change should be defined, authorized for implementation, and documented. Possible changes may include

- new samples with new compounds or new matrices,
- new analysts with different skills,
- new instruments with different characteristics,
- new location with different environmental conditions,
- new chemicals and/or reference standards, and
- modification of analytical parameters.

An evaluation should determine whether the change is within the scope of the method. If so, no revalidation is required. If the change lies outside the scope, the parameters for revalidation should be defined. After the validation experiments, the system suitability test parameters should be investigated and redefined, if necessary.

PARAMETERS FOR METHOD VALIDATION

The parameters for method validation have been defined in different working groups of national and international committees and are described in the literature. Unfortunately, some of the definitions vary between the different organizations. An attempt at harmonization was made for pharmaceutical applications through the ICH (4,5), where representatives from the industry and regulatory agencies from the United States, Europe, and Japan defined parameters, requirements, and, to some extent, methodology for analytical methods validation. The parameters, as defined by the ICH and by other organizations and authors, are summarized in Table 3 and are described in brief in the following paragraphs.

Selectivity/Specificity

The terms *selectivity* and *specificity* are often used interchangeably. A detailed discussion of this term, as defined by different organizations, has been presented by Vessmann (85). He particularly pointed out the difference between the definitions of specificity given by IUPAC/WELAC and the ICH.

Table 3 Possible Analytical Parameters for Method Validation

- Specificity (1,2)
- Selectivity
- Precision (1,2)
  - repeatability (1)
  - intermediate precision (1)
  - reproducibility (3)
- Accuracy (1,2)
- Trueness
- Bias
- Linearity (1,2)
- Range (1,2)
- Limit of detection (1,2)
- Limit of quantitation (1,2)
- Robustness (2,3)
- Ruggedness (2)

1. Included in ICH publications
2. Included in USP
3. Terminology included in ICH publication but not part of required parameters

Although it is not consistent with the ICH, the term *specific* generally refers to a method that produces a response for a single analyte only, while the term *selective* refers to a method that 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 (28) defines the 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. Besides chromatographic separation, the sample preparation step can also be optimized for best selectivity.

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. Therefore, the analyst should know how many compounds are in the sample or whether procedures for detecting impure peaks should be used.

While in the past chromatographic parameters such as mobile phase composition or the column were modified, now the application of

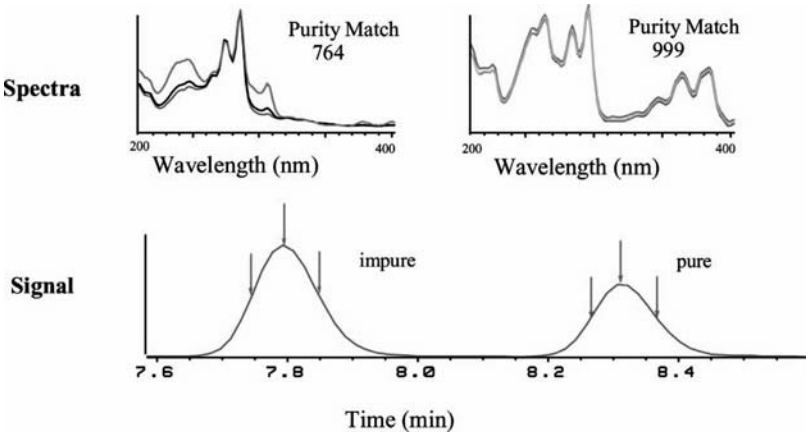


Figure 4 Examples of pure and impure HPLC peaks. The chromatographic signal does not indicate any impurity in either peak. Spectral evaluation, however, identifies the peak on the left as impure. *Abbreviation*: HPLC, high performance liquid chromatography.

spectroscopic detectors coupled on-line to the chromatograph is being used. 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 HPLC and their application and limitations with regard to peak purity are described in the literature (86). Examples of pure and impure HPLC peaks are shown in Figure 4. 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 percent can be detected.

Selectivity studies should also assess interferences that may be caused by the matrix, e.g., urine, blood, soil, water, or food. Optimized sample preparation can eliminate most of the matrix components. The absence of matrix interferences for a quantitative method should be demonstrated by the analysis of at least five independent sources of control matrix.

Precision and Reproducibility

The precision of a method (Table 4) is the extent to which the individual test results of multiple injections of a series of standards agree. The measured

standard deviation can be subdivided into 3 categories: repeatability, intermediate precision, and reproducibility (4,5). Repeatability is obtained when the analysis is carried out in a laboratory by an operator using a piece of equipment over a relatively short time span. At least 6 determinations of 3 different matrices at 2 or 3 different concentrations should be performed, and the RSD calculated.

The ICH (4) requires precision from at least 6 replications to be measured at 100 percent of the test target concentration or from at least 9 replications covering the complete specified range. For example, the results can be obtained at 3 concentrations with 3 injections at each concentration.

The acceptance criteria for precision depend very much on the type of analysis. Pharmaceutical QC precision of greater than 1 percent RSD is easily achieved for compound analysis, but the precision for biological samples is more like 15 percent at the concentration limits and 10 percent at other concentration levels. For environmental and food samples, precision is largely dependent on the sample matrix, the concentration of the analyte, the performance of the equipment, and the analysis technique. It can vary between 2 percent and more than 20 percent.

The AOAC manual for the Peer-Verified Methods program (9) includes a table with estimated precision data as a function of analyte concentration (Table 4).

Intermediate precision is a term that has been defined by ICH (4) as the long-term variability of the measurement process. It is determined by comparing the results of a method run within a single laboratory over a number of weeks. A method's intermediate precision may reflect discrepancies in results obtained

- from different operators,
- from inconsistent working practice (thoroughness) of the same operator,
- from different instruments,
- with standards and reagents from different suppliers,
- with columns from different batches, or
- a combination of these.

The objective of intermediate precision validation is to verify that in the same laboratory the method will provide the same results once the development phase is over.

Reproducibility (Table 5), as defined by the ICH (4), represents the precision obtained between different laboratories. The objective is to verify that the method will provide the same results in different laboratories. The reproducibility of an analytical method is determined by analyzing aliquots from homogeneous lots in different laboratories with different analysts, and by using operational and environmental conditions that may differ from, but

Table 4 Analyte Concentration vs. Precision

Analyte (%)	Analyte ratio	Unit	RSD (%)
100	1	100%	1.3
10	10^{-1}	10%	2.8
1	10^{-2}	1%	2.7
0.1	10^{-3}	0.1%	3.7
0.01	10^{-4}	100 ppm	5.3
0.001	10^{-5}	10 ppm	7.3
0.0001	10^{-6}	1 ppm	11
0.00001	10^{-7}	100 ppb	15
0.000001	10^{-8}	10 ppb	21
0.0000001	10^{-9}	1 ppb	30

Source: Ref 9.

are still within, the specified parameters of the method (interlaboratory tests). Validation of reproducibility is important if the method is to be used in different laboratories.

Table 6 summarizes factors that should be the same, or different, for precision, intermediate precision, and reproducibility.

Accuracy and Recovery

The accuracy of an analytical method is the extent to which test results generated by the method and the true value agree. Accuracy can also be described as the closeness of agreement between the value that is adopted, either as a conventional, true, or accepted reference value, and the value found.

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

Table 5 Typical Variations Affecting a Method's Reproducibility

- Differences in room temperature and humidity
- Operators with different experience and thoroughness
- Equipment with different characteristics, e.g., delay volume of an HPLC system
- Variations in material and instrument conditions, e.g., in HPLC, mobile phases composition, pH, flow rate of mobile phase
- Variation in experimental details not specified by the method
- Equipment and consumables of different ages
- Columns from different suppliers or different batches
- Solvents, reagents, and other material with varying quality

Table 6 Variables for Measurements of Precision, Intermediate Precision, and Reproducibility

	Precision	Intermediate Precision	Reproducibility
Instrument	Same	Different	Different
Batches of accessories, e.g., chromatographic columns	Same	Different	Different
Operator	Same	Different	Different
Sample matrices	Different	Different	Different
Concentration	Different	Different	Different
Batches of material, e.g., reagents	Same	Different	Different
Environmental conditions, e.g., temperature, humidity	Same	Different	Different
Laboratory	Same	Same	Different

the reference method is known. Secondly, accuracy can be assessed by analyzing a sample with known concentrations (e.g., a control sample or certified reference material) and comparing the measured value with the true value as supplied with the material. If certified reference materials or control samples are 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. If validated correctly, the recovery factor determined for different concentrations can be used to correct the final results.

The concentration should cover the range of concern and should include concentrations close to the quantitation limit, one in the middle of the range, and one at the high end of the calibration curve. Another approach is to use the critical decision value as the concentration point that must be the point of greatest accuracy.

The expected recovery (Table 7) depends on the sample matrix, the sample processing procedure, and the analyte concentration. The AOAC manual for the Peer-Verified Methods program (9) includes a table with estimated recovery data as a function analyte concentration.

The ICH document on validation methodology recommends accuracy to be assessed using a minimum of nine determinations over a minimum of three concentration levels covering the specified range (e.g., three concentrations/three replicates each). Accuracy should be reported as percent recovery by the assay of known added amount of analyte in the sample or as the

Table 7 Analyte Recovery at Different Concentrations

Active Ingredient (%)	Analyte ratio	Unit	Mean recovery (%)
100	1	100%	98-102
≥ 10	10^{-1}	10%	98-102
≥ 1	10^{-2}	1%	97-103
≥ 0.1	10^{-3}	0.1%	95-105
0.01	10^{-4}	100 ppm	90-107
0.001	10^{-5}	10 ppm	80-110
0.0001	10^{-6}	1 ppm	80-110
0.00001	10^{-7}	100 ppb	80-110
0.000001	10^{-8}	10 ppb	60-115
0.0000001	10^{-9}	1 ppb	40-120

Source: Ref. 9.

difference between the mean and the accepted true value, together with the confidence intervals.

Linearity and Calibration Curve

The linearity of an analytical method is its ability to elicit test results that are directly proportional to the concentration of analytes in samples within a given range or proportional by means of well-defined mathematical transformations. Linearity may be demonstrated directly on the test substance (by dilution of a standard stock solution) and/or by using separate weightings of synthetic mixtures of the test product components, using the proposed procedure.

Linearity is determined by a series of 3 to 6 injections of 5 or more standards whose concentrations span 80–120 percent of the expected concentration range. The response should be directly proportional to the concentrations of the analytes or proportional by means of a well-defined mathematical calculation. A linear regression equation applied to the results should have an intercept not significantly different from zero. If a significant nonzero intercept is obtained, it should be demonstrated that this has no effect on the accuracy of the method.

Frequently, the linearity is evaluated graphically, in addition to or as an alternative to mathematical evaluation. The evaluation is made by visually inspecting a plot of signal height or peak area as a function of analyte concentration. Because deviations from linearity are sometimes difficult to detect, two additional graphical procedures can be used. The first is to plot the deviations from the regression line versus the concentration or versus the logarithm of the concentration, if the concentration range covers several decades. For linear ranges, the deviations should be equally distributed between positive and negative values.

Another approach is to divide signal data by their respective concentrations, yielding the relative responses. A graph is plotted with the relative responses on the y-axis and the corresponding concentrations on the x-axis, on a log scale. The obtained line should be horizontal over the full linear range. At higher concentrations, there will typically be a negative deviation from linearity. Parallel horizontal lines are drawn on the graph corresponding to, for example, 95 percent and 105 percent of the horizontal line. The method is linear up to the point where the plotted relative response line intersects the 95 percent line. Figure 5 shows a comparison of the two graphical evaluations on a sample of caffeine using HPLC.

The ICH recommends, for accuracy reporting, the linearity curve's correlation coefficient, y-intercept, slope of the regression line, and residual sum of squares. A plot of the data should be included in the report. In addition, an analysis of the deviation of the actual data points from the regression line may also be helpful for evaluating linearity. Some analytical procedures, such as immunoassays, do not demonstrate linearity after any transformation. In this case, the analytical response should be described by an appropriate function of the concentration (amount) of an analyte in a sample. In order to

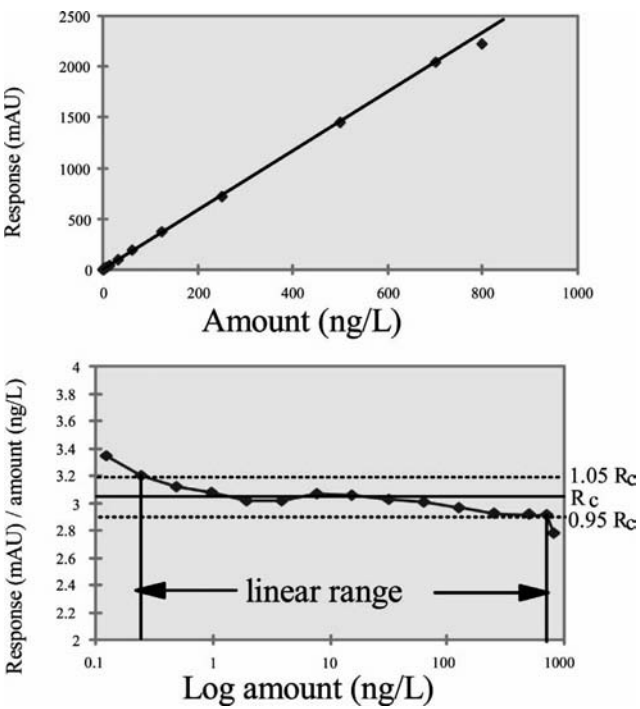


Figure 5 Linearity plot of a caffeine sample using HPLC. *Abbreviation*: HPLC, high performance liquid chromatography.

establish linearity, a minimum of five concentrations is recommended. Other approaches should be justified.

Plotting the sensitivity (response/amount) gives clear indication of the linear range. Plotting the amount on a logarithmic scale has a significant advantage for wide linear ranges.

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 the test results (e.g., percentage, parts per million) obtained by the analytical method.

For assay tests, the ICH (5) requires the minimum specified range to be 80 to 120 percent of the test concentration, and for the determination of an impurity, the range to extend from the limit of quantitation, or from 50 percent of the specification of each impurity, whichever is greater, to 120 percent of the specification.

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. The limit of detection is frequently confused with the sensitivity of the method. The sensitivity of an analytical method is the capability of the method to discriminate small differences in concentration or mass of the test analyte. In practical terms,

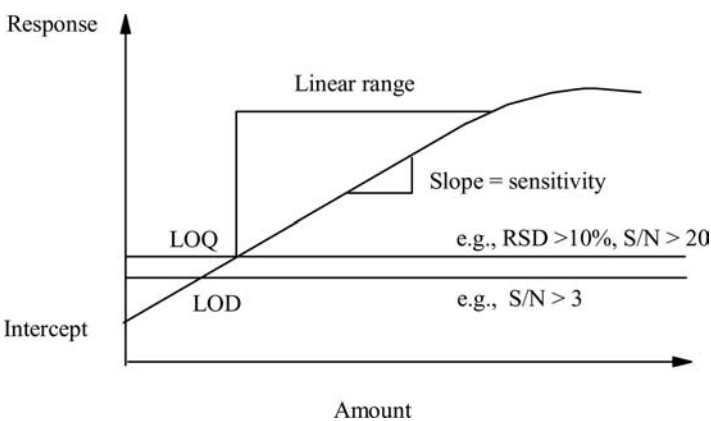


Figure 6 Definitions for linearity, range. *Abbreviations*: LOQ, limit of quantitation; LOD, limit of detection.

sensitivity is the slope of the calibration curve that is obtained by plotting the response against the analyte concentration or mass.

In chromatography, the detection limit is the injected amount that results in a peak with a height at least two or three times as high as the baseline noise level. Besides this signal/noise method, the ICH (4) describes three more methods:

1. *Visual inspection:* The detection limit is determined by the analysis of samples with known concentrations of analyte and by establishing the minimum level at which the analyte can be reliably detected.
2. *Standard deviation of the response based on the standard deviation of the blank:* Measurement of the magnitude of analytical background response is performed by analyzing an appropriate number of blank samples and calculating the standard deviation of these responses.
3. *Standard deviation of the response based on the slope of the calibration curve:* A specific calibration curve is studied using samples containing an analyte in the range of the limit of detection. The residual standard deviation of a regression line, or the standard deviation of y-intercepts of regression lines, may be used as the standard deviation.

Limit of Quantitation

The limit of quantitation is the minimum injected amount that produces quantitative measurements in the target matrix with acceptable precision in chromatography, typically requiring peak heights 10 to 20 times higher than the baseline noise.

If the required precision of the method at the limit of quantitation has been specified, the EURACHEM (Fig. 8) (87) approach can be used. A number

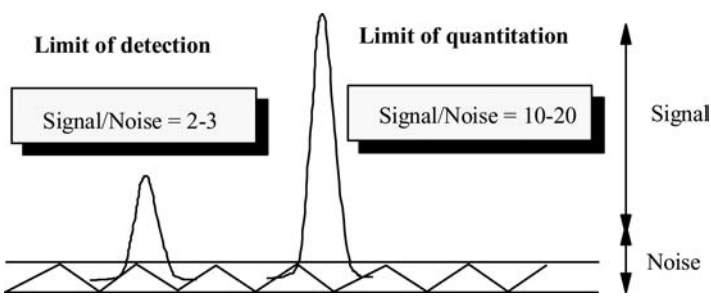


Figure 7 Limit of detection and limit of quantitation via signal to noise.

of samples with decreasing amounts of the analyte are injected six times. The calculated RSD percent of the precision is plotted against the analyte amount. The amount that corresponds to the previously defined required precision is equal to the limit of quantitation. It is important to use not only pure standards for this test but also spiked matrices that closely represent the unknown samples.

For the limit of detection, the ICH (5) recommends, in addition to the procedures as described above, the visual inspection and the standard deviation of the response and the slope of the calibration curve.

Any results of limits of detection and quantitation measurements must be verified by experimental tests with samples containing the analytes at levels across the two regions. It is equally important to assess other method validation parameters, such as precision, reproducibility and accuracy, close to the limits of detection and quantitation. Figure 6 illustrates the limit of quantitation (along with the limit of detection, range, and linearity). Figure 7 illustrates both the limit of detection and the limit of quantitation.

Ruggedness

Ruggedness is not addressed in the ICH documents (4,5). Its definition has been replaced by reproducibility, which has the same meaning as ruggedness, defined by the USP as the degree of reproducibility of results obtained under a variety of conditions, such as different laboratories, analysts, 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.

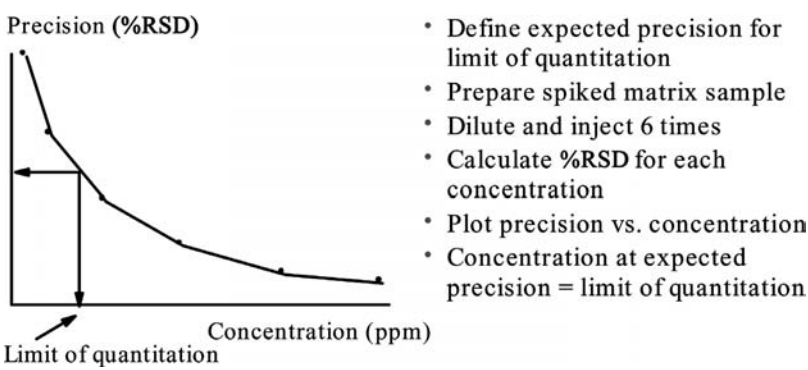


Figure 8 Limit of quantitation with the EURACHEM method. *Abbreviation*: RSD, relative standard deviation. *Source*: Ref. 87.

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 (5), 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 as part of a product registration.

Stability

Many solutes readily decompose prior to chromatographic investigations, for example, during the preparation of the sample solutions, extraction, cleanup, phase transfer, or storage of prepared vials (in refrigerators or in an automatic sampler). Under these circumstances, method development should investigate the stability of the analytes and standards.

The term *system stability* has been defined as the stability of the samples being analyzed in a sample solution. It is a measure of the bias in assay results generated during a pre-selected time interval, for example, every hour up to 46 hours, using a single solution (Fig. 9). System stability should be determined by replicate analysis of the sample solution. System stability is considered appropriate when the RSD, calculated on the assay results obtained at different time intervals, does not exceed more than 20 percent of the corresponding value of the system precision. If, on plotting the assay results as a function of time, the value is higher, the maximum duration of the usability of the sample solution can be calculated.

The effect of long-term storage and freeze–thaw cycles can be investigated by analyzing a spiked sample immediately after preparation and on subsequent days of the anticipated storage period. A minimum of two cycles at two concentrations should be studied in duplicate. If the integrity of the drug is affected by freezing and thawing, spiked samples should be stored in individual containers, and appropriate caution should be employed for the study of samples.

Which Parameters Should Be Included in Method Validation?

For an efficient validation process, it is of utmost importance to specify the right validation parameters and acceptance criteria. The more parameters,

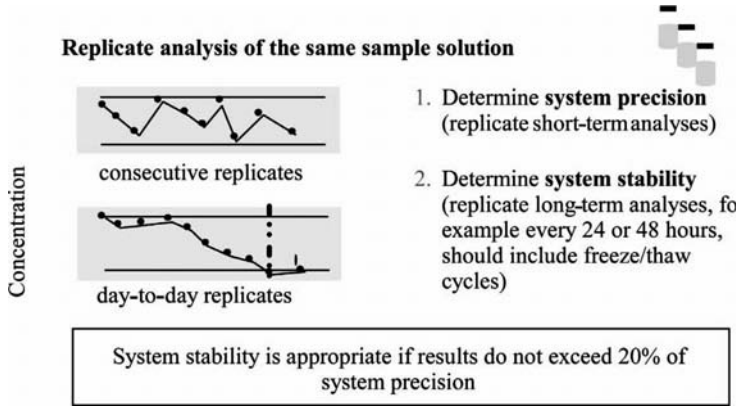


Figure 9 Schematics of stability testing.

the more time it will take to validate. The more stringent the specifications or acceptance limits, the more often the equipment has to be recalibrated, and probably also requalified, to meet the higher specifications at any one time. It is not always essential to validate every analytical performance parameter, but it is necessary to define which ones are required. This decision should be based on business, regulatory, and/or accreditation requirements:

Table 8 ICH Validation Characteristics

		Impurity testing		
Analytical task	**Identification**	**Quantitative**	**Limit tests**	**Assay**
Accuracy	No	Yes	No	Yes
Precision				
Repeatability	No	Yes	No	Yes
Intermediate Precision	No	Yes	No	Yes
Reproducibility	No	No	No	No
Specificity	Yes	Yes	Yes	Yes
Limit of detection	No	No	Yes	No
Limit of quantitation	No	Yes	No	No
Linearity	No	Yes	No	Yes
Range	No	Yes	No	Yes

Abbreviations: ICH, International Conference on Harmonization.

Table 9 USP Characteristics

Analytical task	Assay Category 1	Assay category 2		Assay Category 3
		Quantitative	Limit tests	
Accuracy	Yes	Yes	*	*
Precision	Yes	Yes	No	Yes
Specificity	Yes	Yes	Yes	*
Limit of detection	No	No	Yes	*
Limit of quantitation	No	Yes	No	*
Linearity	Yes	Yes	No	*
Range	Yes	Yes	*	*
Ruggedness	Yes	Yes	Yes	*

*May be required, depending on the nature of the specific test. *Abbreviation*: USP, United States Pharmacopeia.

1. For contract analyses: What does the client request?
2. For regulatory submission: What do the regulations or guidelines require?
3. For laboratory accreditation: What do the standard and relevant guidelines recommend?

The validation parameters depend on the analytical task and the scope of the method. For example, both the USP (28) and the ICH (4) contain chapters on validation procedures for different analytical tasks, both of which are included to provide some ideas on what type of validations are required for different tasks (see Tables 8 and 9). For example, according to the ICH, accuracy, any type of precision and limits of detection and quantitation are not required if the analytical task is identification. For assays in USP category 1, the major component or active ingredient to be measured is normally present at high concentrations; therefore, validation of limits of detection and quantitation is not necessary.

Because the type of analysis and the information that should be obtained from a sample have so much influence on the validation, the objective and scope of the method should always be defined as the first step of any method validation.

Summary Recommendations

1. Develop a validation master plan or an operating procedure for method validation.

2. For individual method validation projects, develop a validation project plan.
3. Define intended use of the method and performance criteria.
4. Check all equipment and material for performance and quality.
5. Perform validation experiments.
6. For standard methods: check scope of the standard with your own requirements.
7. For non-routine methods: develop and use generic methods and customize them for specific non-routine tasks.
8. Develop an operating procedure for method transfer between laboratories.

12

Data Review and Validation and Evaluation of Uncertainty

What Is Discussed in this Chapter?

1. How to review data
2. How to validate data
3. How to identify the contribution of different effects to overall measurement uncertainty
4. How to estimate measurement uncertainty
5. How to report test results

Data validation is the process by which data are reviewed, checked for plausibility and accuracy, and accepted or rejected based on defined procedures. It is also the final step before release of test results. The following points should be considered:

- SOPs should exist for the definition of raw data, data entry, security, and review.
- The accuracy of critical data should be verified, irrespective of whether the data were entered manually or were transferred electronically from an analytical instrument.
- Checks, preferably performed automatically, should be built into any routine method to identify errors. Requirements for a validity check of data include well-maintained instruments, documented measurement processes, and statistically supported limits of uncertainty.
- Final results should be traceable back to the individual who entered the data, or, in cases where data are acquired on-line from an

analytical instrument, the instrument should be identified. In the latter case, it is recommended to store the instrument serial number, method parameters, and instrument conditions together with the raw data.

- Any failure or unforeseen event that has occurred with the instrument should be recorded automatically in a log-book and stored together with the raw data. The impact of the error on the data should be evaluated and suitable action taken.
- If changes have been made to any data, the original raw data should not be obscured by these changes. The person who made the change must be identified, and the reason for the change should be given together with the date.
- Quantitative data reports should include a statement on the measurement uncertainty. This is the estimate attached to a measurement characterizing the range of values within which the true value is purported to lie (ISO/DIS 3354-1).

This chapter discusses techniques for data review and validation. It also describes procedures to measure uncertainty and recommends the contents for an analysis report.

VALIDATION OF DATA

Data should be reviewed and validated by a qualified and authorized person following an SOP. A prerequisite for accurate data analysis is that the instrument is functioning properly and test methods are validated. Preventive maintenance, together with regular calibration and performance verification and system suitability testing, facilitates the instrument's ability to generate accurate test results.

Checks should be made for

- proper sample identification,
- transmittal errors,
- plausibility, and
- consistency.

Techniques used to accomplish this include

- comparisons with similar data,
- checks for plausibility of values with respect to specified limits,

- regression analysis, and
- tests for outliers.

Checks, preferably automated, should be built into any routine method to identify errors. In chromatography and capillary electrophoresis, baseline stability, peak shape, resolution, peak identification, and integration marks should be checked to ensure that peaks are suitable for quantitative analysis.

Two frequent points of discussion are how and how many data should be validated. The answer depends on the analysis task, the analysis method, and the probability of obtaining any incorrect data. Let's take the example of a biological sample that is analyzed using HPLC and UV detection. If the analytes are expected to be present close to the detection limits and could possibly interfere chromatographically with the chemical matrix, there is a high risk of wrong identification, integration, and quantitation. In this case, it is recommended to inspect every chromatogram visually and to reintegrate if necessary. A 100 percent check of chromatograms is not worth doing, however, for well-defined samples with only a few, well-separated peaks and where the expected amounts are far above the limit of quantitation. Both a good understanding of the analysis task and knowledge of the measurement process, together with a realistic notion of anticipated problems supported by statistical data, are the basis for a sound scientific judgment of the extent of data validation.

REPORTING DATA

The type of information that is reported depends very much on the individual situation.

The results of each test should be recorded accurately, unambiguously, and objectively and in accordance with any specific instructions in the test methods and requested by customers.

Paragraph 5.10.1 of the ISO/IEC standard 17025 (53) gives very specific guidelines on the minimal contents of a report. A template with report items is shown in Figure 1.

The report should include the following:

- name and address of the laboratory
- identification of sample and test items
- methods for sampling and analysis
- test results and the expected uncertainty
- names, function, and signatures of person authorizing the test report
- page number and total number of pages

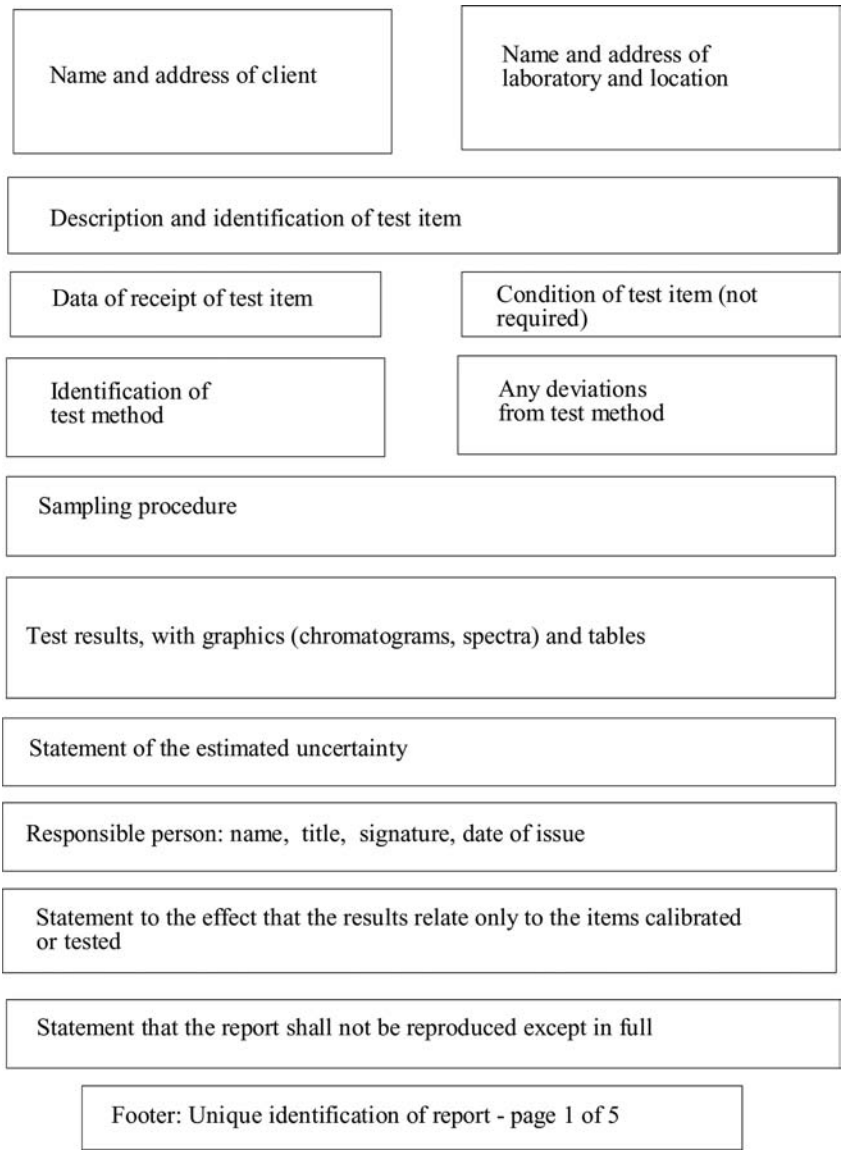


Figure 1 Example for report template with the 15 report items.

While the headings should be standardized as much as possible, the presentation of the actual test results should be specifically designed for each type of test and should be easy to understand for the reader.

ISO 17025 suggests additional information on a case-by-case basis.

- For nonstandard methods: a brief description of the method.
- Deviations from, additions to, or exclusions from the test method.
- For reports containing the results of sampling: unambiguous identification of substance, matrix, material, or product sampled; location of sampling; details of any environmental conditions during sampling that may affect the interpretation of the test results; and a reference to the sampling method.

MEASUREMENT AND REPORTING OF UNCERTAINTY

Every measurement has an uncertainty associated with it that results from errors arising at the various stages of sampling, sample injection, measurement, and data evaluation. In other words, whenever any quantitative measurement is performed, the value obtained is only an approximation of the true value. Users of the measurement data should have an idea of how much the reported result may deviate from the true value. In practice, all accreditation standards and quality standards such as ISO/IEC 17025 (53) and the EURACHEM/CITAC guide (31) recommend the results of quantitative measurement to be reported as both a single value and together with the possible deviation from the true value. This is the measurement uncertainty. This is logical for any report with quantitative results. It is, for example, of no use if a report on a food sample refers to "0.1 percent of compound X," and the user of the data is still unsure whether this could be 0.05 or 0.4 percent. An uncertainty statement provides the user with information on the measurement tolerances and the limits within which the true value of the measurement, such as analyte concentration, is supposed to lie. Frequently, the analyst can make a good estimate of the level of uncertainty; the client or user of the data, however, cannot.

In Paragraph 5.4.6.2, the ISO/IEC Standard 17025 (53) contains a statement about measurement uncertainty:

> *Testing laboratories shall have and shall apply procedures for estimating uncertainty of measurement.*

And 5.10.3.1 states:

> *Where applicable, the report shall include a statement on the estimated uncertainty of measurement, information on uncertainty is needed in test reports when it is relevant to the validity of application of the test results, when customer's instruction so requires, or where uncertainty affects compliance to a specification limit.*

Information on uncertainty is of particular importance if a specification limit is to be verified and reported. For example, if, according to a purchasing agreement, a product can only be released if compound X is below 0.5 percent, the test report may not contain a statement about compliance if the measurement results extended by the measurement uncertainty are above 0.5 percent.

When parameter(s) are claimed to be within specified tolerance, the measurement value(s) extended by the estimated uncertainty of measurement shall fall within the specification limit.

While it is clearly understood that the measurement tolerances should be known and also reported if the client requests these data, there is dissatisfaction among chemists with the word *uncertainty* itself. "Uncertainty" is a negative

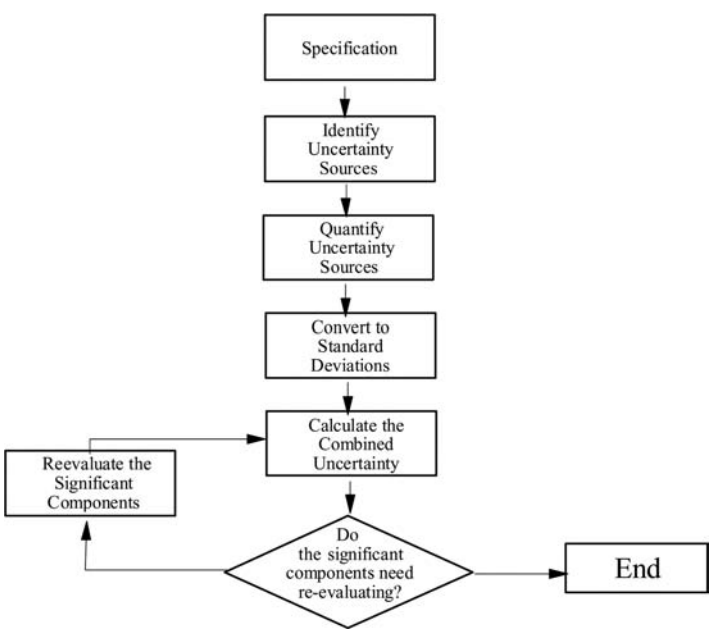


Figure 2 The uncertainty estimation process. *Source*: Ref. 89.

word and is usually associated with "doubt." This could cast doubt not only on the result but also on the measurement technique, the equipment used, the instrument operator, or even the laboratory. Using more positive-sounding words, such as analysis confidence, would create a more positive approach. However, the word *uncertainty* is now well established and should be used whether we like it or not.

ISO has published a *Guide to the Expression of Uncertainty in Measurement* (88). It establishes general rules for evaluating and expressing uncertainty in measurement across a broad spectrum of measurements.

EURACHEM has produced an excellent document containing many more details on how the concepts of the ISO guide may be applied in chemical measurement. The whole process is schematically shown in Figure 2. The basic ideas are explained in this chapter, but for more detailed information, readers of the book are encouraged to study the EURACHEM document (89).

The concept of evaluating uncertainty is fairly straightforward. It requires a detailed knowledge of the nature of the measurand and of the measurement method, rather than an in-depth understanding of statistics. The following steps are recommended:

1. Develop the specifications by writing a clear statement of exactly what is to be measured and the relationship between this and the parameters on which it depends. For example, if the measurement temperature has an influence on the result, the measurement temperature should also be defined.
2. Develop a workflow diagram for the entire sampling, sample preparation, calibration, measurement, data evaluation, and data transcription process.
3. Identify and list sources of uncertainty for each part of the process or each parameter. Possible sources for errors may be derived from nonrepresentative sampling, operator bias, a wrongly calibrated instrument, lack of ideal measurement conditions, chemicals with impurities, and errors in data evaluation.
4. Estimate and document the size of each uncertainty, for example, as standard deviations or as RSDs. These data should be gathered from a series of measurements. Where experimental evaluation is impossible or impractical, the individual contributions should be estimated from whatever sources are available. Sources for this kind of estimation can be found in the supplier's information or in the results of interlaboratory studies or proficiency testing. The procedures and thoughts behind the way the contributions have been measured or estimated should be documented.

5. Combine separate contributions in order to give an overall value. For example, where individual sources of uncertainty are independent, the overall uncertainty can be calculated as a multiple of the sum of squared contributing uncertainty components, all expressed as standard deviations. Computer software or spreadsheet programs can help to automate this calculation.

The whole procedure should be documented in such a way that sufficient information is available to allow the result to be re-evaluated if new information or data become available. A complete documentation should include

- a description of the methods used to calculate the measurement result and its uncertainty from the experimental measurements,
- the values and sources of all corrections, and
- a list of all components of uncertainty with full documentation on how each of these was evaluated.

For routine sample analysis, the uncertainty measurement may take place at the end of method validation, before a validated method is used in a laboratory and at discrete intervals. For non-routine methods, adequate investigation of similar analysis procedures may be sufficient.

Reference 104 includes many practical examples with data from different analyses, as well as formulas for evaluating, calculating, and reporting standard and expanded uncertainty. Reports of sample analysis should include an uncertainty number, which is typically expressed as

$$\begin{aligned} \text{Result} &= x \pm u \text{ (units)} \\ \text{or} & \\ \text{Result} &= x \text{ (units)} \\ \text{Uncertainty} &= u \text{ (units)} \end{aligned}$$

Summary Recommendations

1. Develop a general procedure for data validation, traceability, and security type.
2. Identify the specific data validation need for each analysis

3. Develop a general template for reporting. Using this template as a basis, agree with the user of the data on the specific content of the report.
4. Evaluate and report the uncertainty of the overall sampling and analysis procedure. Evaluation can be done during and after method validation and at discrete intervals.

13

Handling Out-of-Specification Situations

What Is Discussed in this Chapter?

1. FDA and international requirements
2. How to conduct laboratory failure investigations
3. Responsibilities of analysts, laboratory supervisors, and quality control
4. Tracking and trending OOS results
5. How to deal with out-of-trend (OOT) results
6. Developing corrective and preventive action plans
7. Strategies to avoid OOS situations before they occur

The FDA and other agencies require that an investigation be conducted whenever an Out-of-Specification (OOS) test result is observed. For example, 21 CFR 211.192 states:

All drug product production and control records, including those for packaging and labelling, shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed. Any unexplained discrepancy (including a percentage of theoretical yield exceeding the maximum or minimum percentages established in master production and control records) or the failure of a batch or any of its components to meet any of its specifications shall be thoroughly investigated, whether or not the batch has already been distributed. The investigation shall extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. A written record of the investigation shall be made and shall include the conclusions and follow-up.

In 2006, the FDA released a final guidance document (26), which provided the Agency's current position on evaluation of suspect, or OOS, test results. According to this document, OOS results include those that fall outside the specifications or acceptance criteria established in New Drug Applications (NDAs), official compendia, or by the manufacturer. Test results that fall outside historical, expected, or previous trends are suspect results and also require investigation.

The guidance applies to laboratory testing during the manufacture of Active Pharmaceutical Ingredients (APIs) and other components, and the testing of finished products to the extent that cGMP regulations apply. It also applies to raw material, in-process material, and stability testing. Specifically, the guidance discusses how to investigate suspect or OOS test results, including the responsibilities of laboratory personnel during the laboratory phase of the investigation, additional testing if necessary, expansion of the investigation outside of the laboratory, and final evaluation and reporting of all test results. The guide also applies for contract laboratories that perform testing of starting materials, packaging materials, intermediates, and/or finished products.

The guidance makes it clear that the main purpose of an investigation is to determine the cause of an OOS. An investigation is also necessary if the batch is rejected.

> *The purpose of the investigation is to determine the cause of the OOS. Even if a batch is rejected based on an OOS result, the investigation is necessary to determine if the result is associated with other batches of the same drug product or other products. Batch rejection does not negate the need to perform the investigation.*

The FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories (22) also has a section on OOS. The guide specifies a time frame for the investigations:

> *· · · all failure investigations should be performed within 20 business days of the problem's occurrence and recorded and written into a failure or investigation report).*

It also requires corrective measures and an action plan to prevent recurrence:

> *Outline corrective actions necessary to save the batch and prevent similar recurrence.*

The FDA's industry guidance Quality Systems Approach to Pharmaceutical cGMP recommends investigations and corrective actions as part of the quality systems.

> *A key component in any quality system is handling nonconformities and/or deviations. The investigation, conclusion, and follow-up should be documented. Corrective action is a reactive tool for system improvement to ensure that significant problems do not recur.*

International guidelines also have chapters on handling, documentation, and follow-up of OOS results. For example, the ICH Q7A guide on Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients (49) states:

> *Any out-of-specification result obtained should be investigated and documented according to a procedure. This procedure should include analysis of the data, assessment of whether a significant problem exists, allocation of the tasks for corrective actions, and conclusions. Any resampling and/or retesting after OOS results should be performed according to a documented procedure*

There are numerous publications about OOS results and failure investigations. A comprehensive approach of OOS results, from failure investigations to corrective and preventive actions, is offered in a primer dedicated exclusively to this topic.

Lanese (91) provided an update of the current FDA position, including a descriptive flowchart on handling OOS investigations. Most authors offer recommendations on what to do when an OOS result occurs. However, there is no clear guideline available on how to avoid or minimize OOS results. In addition to being very expensive, OOS should be avoided because frequent or repetitive occurrence is a clear indication of quality system performance problems. Based on these considerations, Huber (92) published a paper on how to prevent OOS situations, identifying methods that support a proactive approach instead of the reactive one.

An OOS can be caused by production process errors or laboratory errors. This chapter gives an overview of the complete OOS results investigation, with emphasis on laboratory failure investigations. More details can be found in a primer authored by Huber (93). Portions of that document have been reprinted in this chapter with permission.

OOS RESULTS OVERVIEW

OOS and failure investigations can be best illustrated through flow charts. The flow chart in Figure 1 illustrates the complete procedure from identification of an OOS result to failure investigations and corrective and preventive actions.

According to the FDA guide, the identification of an OOS result should be followed by an investigation to determine the cause of the OOS result. Raw materials, active pharmaceutical ingredients (API), and finished products are tested against product specifications: for example, the amount of individual impurities in finished products should be below 0.1%.When the results are within specifications, they are reported and then reviewed by the laboratory supervisor and the responsible person in quality control for batch disposition purposes. When the test results are outside the predetermined specifications, a laboratory investigation is initiated to identify the source of the problem. If a laboratory error cannot be identified, it is assumed to be a production-related problem and the batch cannot be released at the time. In this case, a multidisciplinary investigation or full-scale OOS investigation is initiated to identify the root cause of the problem, if possible, and initiate appropriate corrective and preventive actions. If a manufacturing error is identified, a corrective action plan is initiated to ensure prevention of recurrence of a similar problem in future batches. As part of the investigation, at this point, an evaluation of the impact of the OOS result on already distributed batches has

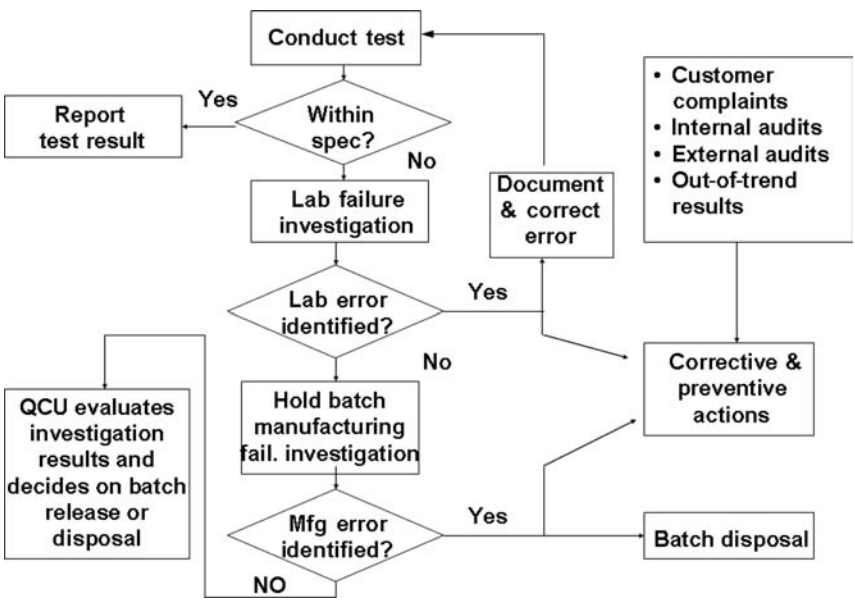


Figure 1 Out-of-specification overview. *Source*: Ref. 95.

to be performed. Simultaneously, a plan is developed to prevent occurrence of the same problem in similar processes.

Phase I: Laboratory Investigation

Figure 2 presents in detail the laboratory investigation process. If there is an OOS situation, the analyst goes through each step of the analysis and checks if a problem occurred, either with the sample, with any equipment, or whether there was a mistake during test execution.

The use of a checklist is strongly recommended for efficiency and completeness. When an OOS result is identified, the supervisor is notified and an assessment of the accuracy of the results has to start as soon as possible. The guidance is specific about the responsibilities of the lab supervisor, providing the steps that should be followed and that refer to the interview of the analyst (to determine analyst ability to perform the test), verification of calculations accuracy, testing instruments performance verification (check for eventual equipment malfunctions recorded in the equipment logbook), appropriateness of standards, reagents, and test method performance.

If a lab error is found that could be a clear cause for the wrong result, the cause is documented and corrected and the same or a second analyst repeats

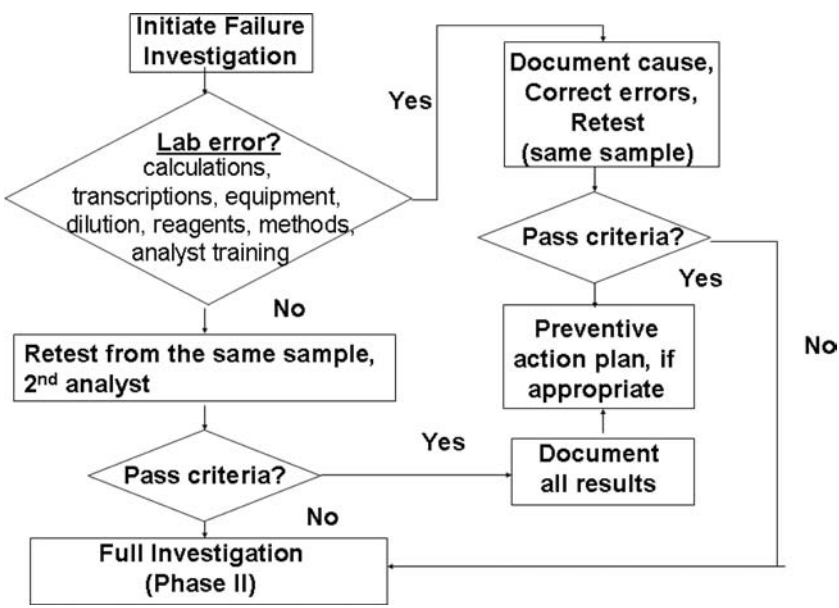


Figure 2 Laboratory failure investigation.*Source*: Ref. 95.

the analysis on the same sample. In some very obvious cases a complete retest is not necessary. For example, if the OOS result was caused by a transcription error, the results are recalculated and reported using the correct transcription and the original result can be invalidated.

If no laboratory error is identified during the laboratory failure investigation, a phase II full-scale investigation is initiated. It is not the scope of this book to elaborate on the multifunctional investigation that encompasses a review of the manufacturing process and/or additional laboratory work. Information on phase II investigations can be found in reference 95.

Responsibilities

Tasks and responsibilities of the analyst, supervisor, Quality Assurance, and Quality Control Unit should be clearly defined in SOPs.

Responsibilities of the analyst include:

- Perform the test correctly
- Be aware of potential problems
- Follow SOPs
- Follow good science
- Discontinue testing in case of an obvious error
- Inform supervisor about an OOS result
- Retain test preparations until data is reviewed and the investigation is completed
- Conduct and document OOS result investigations (joint activity between analysts and supervisor)

Tasks of the supervisor include:

- Review and acceptance or reject of test results
- Conduct laboratory investigation in conjunction with the analyst (assess each step of analysis from sample preparation to sample analysis and data reporting and evaluation)
- Conduct the failure investigation efficiently, thoroughly, and objectively
- Inform the QCU Manager about an OOS situation
- Help with the performance of phase II full-scale investigation
- Provide resources for the development and implementation of corrective and preventive actions (when the OOS is a result of a laboratory error)

Tasks of Quality Assurance include:

- Review and approve procedures
- Verify that procedures are followed
- Consult QCU on decisions regarding batch release

Tasks of the Quality Control Unit include:

- Evaluate OOS phase I and phase II investigations
- Disposition of batches based on the evaluation of OOS investigation results

PREVENTING OUT-OF-SPECIFICATION SITUATIONS CAUSED BY LABORATORY ERRORS

To avoid OOS investigations as much as possible, laboratories are advised to establish a structured OOS preventive program. As a starting point, it is a good idea to look at past OOS situations and possible causes. Common laboratory errors are

- Lack of laboratory data integrity
- Inappropriate use of standards
- Lack of appropriate stability program
- Equipment cleaning test method not appropriately validated
- Instrument errors
- Software errors
- Glassware contaminated
- Method validation not appropriate, (e.g., missing ruggedness tests)
- Inadequately trained laboratory personnel
- Human errors, (e.g., an analyst does not follow the method of analysis, transcribes data wrongly, or uses incorrect standards)

Many of these problems can be avoided by establishing good validation practice as discussed throughout this book. Following these practices, the number of OOS situations will decrease significantly.

Usage and Performance-based Preventative Maintenance

One common reason for laboratory errors is that the maintenance parts deteriorate before they are replaced as part of the preventive maintenance program. This can happen when the number of samples increases and instrument usage is higher than anticipated. Traditionally, maintenance parts are replaced on

a regular schedule. If the usage of the instrument increases with time, maintenance may be carried out too late to avoid errors. Therefore, it is better to exchange maintenance parts based on the time they are used, for example, on a High Performance Liquid Chromatography (HPLC) detector when the lamp is switched on.

Modern instruments can measure the time when the instrument is in use, and the user can set limits, for example, on an HPLC system for the lamp, the amount of solvent pumped, and the number of injections performed. The instrument records the time usage and, if the limits are exceeded, alerts the user that maintenance is required. This allows timely exchange of the maintenance parts before the instrument performance drops below the acceptable limit. The elapsed time after which maintenance should be carried out depends on the particular application. For example, the time an HPLC pump seal should be exchanged depends on the mobile phase. The lamp life of an HPLC Ultraviolet (UV) detector depends on the level of baseline noise that is still tolerable for a specific application. The best usage time for a specific part and application should be taken from experience. This certainly supports one of the requirements of the FDA's OOS draft guidance (26):

> *The analyst should be aware of potential problems that could occur during the testing process and should watch for problems that could create OOS results.*

In some instances, the instrument as part of a self-diagnosis can also measure the correct function of a maintenance part by measuring its performance characteristics. For example, a detector lamp can measure the intensity automatically and inform the user on the result through the user interface. There should be an SOP that requires the user to change the lamp if the intensity falls below a previously specified number.

Performance-based Control Charts

Analysis of quality control samples with quality control charts has been suggested as a way to incorporate quality checks on results as they are being generated (for more details see chapter 9 of this book). Such tests can then detect the values that may be erroneous for any of the following reasons:

- Sample handling processes
- Poor equipment performance
- Reagents are wrongly mixed due to operator error

- Reagents are contaminated
- Gas Chromatograph (GC) carrier gas is impure
- Instrument characteristics have changed over time
- Operator training and errors
- Chromatographic column characteristics have changed
- Deficiency of material (e.g., HPLC mobile phase is contaminated)

The purpose of quality control charts is to identify a problem as quickly as possible, preferably before an OOS occurs. Corrections can be taken that require much less time than conducting an OOS investigation.

Identification of Critical System Parameters

The principle of using quality control samples and control charts can be applied to monitor critical system characteristics that can cause OOS situations. Deciding which parameters are critical depends on the system itself. Those chosen parameters should include characteristics that can change over time and have an impact on the decision based on the test results. Critical parameters should be determined based on experience with the system as part of a Failure Modes and Effect Analysis (FMEA).

For example, in chromatography, the most critical element is the chromatographic column. The performance characteristics of the column change over time, for example, the plate number, the selectivity, or the peak symmetry. These characteristics have an impact on the resolution between two peaks and the peak tailing, and both can have an impact on quantitative results.

Automated on-line measurement and plotting of these parameters provide useful hints as to when the systems approach the limits of specified ranges. Corrective action can then be initiated before wrong data are measured. In liquid chromatography, if the resolution between two peaks drops below a specified limit or the tailing factor goes above a certain limit, the results are most likely incorrect and the column needs to be changed. In this way, critical analytical process parameters are measured, plotted, and monitored by the analyst, and/or automatically by a computer control program. Control charts identify when the system reaches critical limits. Ideally, software should allow warning and action limits for each parameter. The actual values should be determined during method validation. To measure these characteristics, either a dedicated quality control sample or the calibration sample can be used. If the calibration sample is used, there is no time lost for additional analysis runs. With appropriate software, the instrument measures the critical characteristics on-line, enters them into a database, and plots the results on a control chart indicating warning limits and control limits. These limits are based on experience with the system or determined during method validation ruggedness tests.

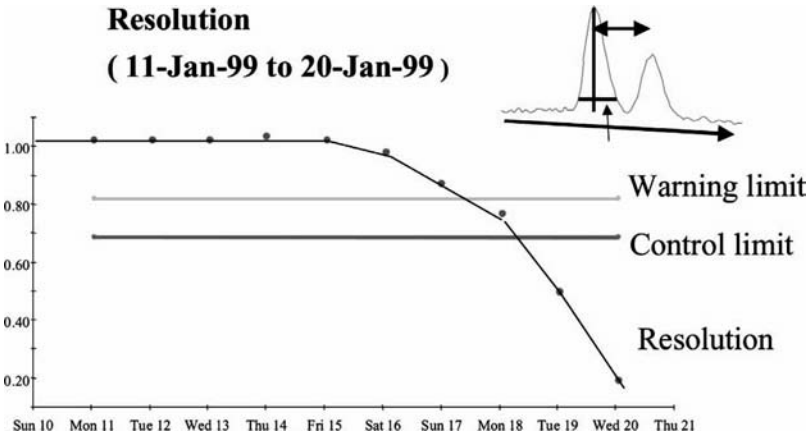


Figure 3 Control chart with peak resolutions and warning and action limits.

Having critical parameters under control makes OOS failure investigations much simpler and less time consuming (if they still occur at all), because most common problems can be avoided. Failures attributed to equipment, method, analysts, or material can be identified more easily.

The concept and examples of HPLC peak resolution is shown in Figure 3. We know from method development experiments that accurate quantitative results cannot be achieved if the resolution between two peaks falls below 1.7. The resolution is mainly a function of mobile phase composition and column characteristics. Exact column lifetime with full performance is not predictable. Using the concept of performance-based control charts we measure and plot the peak resolution every day. As shown in Figure 3, everything worked fine until Friday 1/15. The resolution decreased on 1/16 and further on 1/17 to a level which came close to the previously specified warning limit. On 1/18, the resolution decreased to a level below the warning limit and on 1/19 and 1/20, below control limits with the high risk that the system reports an OOS situation. In this case, the preventive action plan would have required the operator to exchange the column on 1/18 and to run the control sample again. If the resolution was not at the original value, the HPLC system would have to be diagnosed to check if the pump delivered the correct mobile phase composition. An OOS situation may have been avoided.

CORRECTIVE AND PREVENTIVE ACTION PLANS

The FDA expects companies to identify the root cause of a problem that caused the OOS situation and, once it has been found, to initiate corrective and

preventive actions. For example, the FDA Guide "Quality Systems Approach to Pharmaceutical CGMP Regulations" has a section on corrective and preventive actions:

CAPA is a well-known CGMP regulatory concept that focuses on investigating, understanding, and correcting discrepancies while attempting to prevent their recurrence.

> *Quality system models discuss CAPA as three separate concepts, all of which are used in this guidance: Remedial corrections of an identified problem, Root cause analysis with corrective action to help understand the cause of the deviation and potentially prevent recurrence of a similar problem and Preventive action to avert recurrence of a similar potential problem (27).*

The ISO/IEC standard 17025 (52) has several sections on corrective and preventive actions. For example, section 4.10.1 states: "The laboratory shall establish a policy and procedure and shall designate appropriate authorities for implementing corrective action when nonconforming work or departures from the policies and procedures in the quality system or technical operations have been identified."

The standard also suggests determining the root cause of the problem. "The procedure for corrective action shall start with an investigation to determine the root cause(s) of the problem. The need for preventive actions is stated in section 4.11.1:

> *Action plans shall be developed, implemented and monitored to reduce the likelihood of the occurrence of the non conformances and take advantage of the opportunities for improvements.*

A correction plan is necessary to fix the already occurred problem; based on the root or probable cause, corrective actions should be determined to prevent recurrence of similar situations. If the quality issue is systemic, preventive actions should be implemented to prevent occurrence of the same problem on similar processes and equipment.

Corrective and preventive actions should be part of the company/laboratory's quality system and should be documented. It does not only apply for OOS situations but also to the handling of other quality problems, for example, customer complaints and deviations found in annual reviews and in internal and external audits.

Bodea published several papers on the development and maintenance of CAPA as a fundamental quality subsystem (94,95).

The main elements of a CAPA program include:

1. Identification—clearly define the problem (accurate description of the quality problem)
2. Evaluation—appraise the magnitude and impact (risk assessment)
3. Analysis—perform a thorough assessment (Root Cause Analysis)
4. Action Plan—create a list of required tasks (identification of appropriate Correction, CA and PA, team for implementation, completion date and effective date)
5. Implementation—execute the action plan (plan implementation as approved, timely)
6. Effectiveness verification—verify the effectiveness of implemented actions (effectiveness on removing root cause to prevent recurrence)

When implemented correctly, a CAPA program continuously improves the quality of analytical laboratories and also contributes to the decrease of OOS situation incidence.

TRACKING AND TRENDING OF OOS INVESTIGATIONS

Current guidelines do not provide detailed instructions on how to track and trend OOS investigation data, yet the recommendation is in the FDA's OOS guidance (26):

> *Laboratory management should be especially alert to developing trends.*
>
> *Laboratory error should be relatively rare. Frequent errors suggest a problem that might be due to inadequate training of analysts, poorly maintained or improperly calibrated equipment, or careless work. Whenever laboratory error is identified, the firm should determine the source of that error and take corrective action to ensure that it does not occur again to prevent recurrence. To ensure full compliance with the cGMP regulations, the manufacturer also should maintain adequate documentation of the corrective action.*

The excerpts above recommend that developing trends be detected, frequency of lab errors be determined, the reason for lab errors be tracked, corrective actions taken be documented, and effectiveness of the corrective action be ensured.

The recommendation is to track OOS investigation data by the

- type of activity during which the result was identified (in process, release, stability, R&D),
- reason for investigation (nature of event/failure/test type),
- cause code and sub-cause code (e.g., analyst – not following test instructions, not paying attention to detail; training – no training, inadequate training, analyst with insufficient practical experience; testing equipment – out of calibration, defective, etc.),
- timeliness (time to initiate and complete the investigation),
- total number of investigations initiated and closed in a time frame,
- total number of batches affected,
- remedy and prevention (Corrective Actions and/or Preventive Actions), and
- total number of confirmed OOS results.

The information above, when used properly, is of great help in determining the root causes. A suggestion is to look at data from different categories and thus correlate the information obtained by combining categories (e.g., product and cause, product and event, confirmed laboratory error by product and event, confirmed non-laboratory error by product and event). A definition and criteria for trend has to be established. Some possible criteria could be a defined number of results above the average (e.g., 6 consecutive), a defined number of increases or decreases in a row (e.g., 6 consecutive results still within the limit, but increasing, tending to reach the upper or lower acceptance limit), and one occurrence is outside 3 sigma range.

A trend analysis of OOS investigations should respond to key questions to ensure an objective analysis of data, rationale, use of resources, etc.: How is the significance of a trend determined? What investigative action must be taken for a confirmed significant trend, and how will that investigation be tracked? What preventive action, if any, must be taken to eliminate a significant trend, and how will that action or lack of action be documented?

A significant trend must be investigated to determine the risk of reoccurrence of a potential nonconformity and, subsequently, deriving from this, identify and implement a preventive action.

Tracking and trending frequency has to be established by each company depending on the magnitude and specificity of activity.

Summary Recommendations

1. Develop a procedure for handling out-of-specifications situations.
2. Develop a procedure for corrective and preventive action plans

3. If an OOS situation is identified, the analyst starts a laboratory failure investigation.
4. The analyst discusses the findings with the supervisor.
5. If no laboratory error is identified, escalate the investigation to manufacturing.
6. If a laboratory error is found, identify the root cause and initiate and implement corrective and preventive actions (CAPA).
7. Evaluate the effectiveness of the corrective and preventive actions.

14

(Certified) Reference Standards

What Is Discussed in this Chapter?

1. Terminology of (certified) reference material; standard reference material; primary, secondary, and working standards
2. Regulatory and standard requirements
3. Requirements for (certified) reference material
4. Requirements for traceability to national or international standards
5. How to prepare homemade reference material and working standards

INTRODUCTION

The goal of any analytical measurement is to obtain accurate, reliable, and consistent data. Prerequisites for achieving accurate results in analytical laboratories are correct sampling, correct weighing of the sample and standards, well-maintained and calibrated equipment, qualified operators, validated methods, and procedures for data validation. Most important is the use of accurate standards or (certified) reference materials. No matter how skilled the analysts are or how sophisticated and automated the equipment, if the calibration of the system is incorrect, the analytical result will always be wrong.

Even though the chief role of reference materials is to ensure accuracy for a specific method, there is another equally important use of such materials: They enable the laboratory and a specific user to verify the performance of equipment, systems, procedures, and analysts at any time.

Agreement in analysis results with the certified value proves that not only the method is right, but also the equipment and the chemicals used for sample preparation are right and that the operator did a good job. The laboratory can conclude that the data generated for this particular procedure are

correct. All laboratories obtaining the same results are "intercalibrated" and in line with the technically competent organization that certified the material. Any disagreement between the certified value and the value determined by the laboratory indicates a problem with the analysis, which then requires a thorough follow-up.

Users may encounter several problems with (certified) reference standards.

- As there are many compounds, it may be difficult to purchase reference materials for all compounds.
- Even if the compound may be available, the sample matrix may be different from the matrix of the reference materials.
- The concentration may differ.
- Chemical standards may have a limited lifetime.
- Traceability is not always possible.

Because of the importance of reference materials in the overall qualification process and the many problems analysts have with them, this chapter is dedicated to this topic. Frequently asked questions are as follows:

- What is the difference between a reference material and a certified reference material?
- What is the relation to primary, secondary, and in-house or working standards?
- When do I need certified reference materials?
- What do regulations and standard guidelines say?
- Do I need traceability to national or other standards?
- What do I do in case there are no certified standards available?
- How do I prepare working standards in my lab?
- How can I ensure the quality of the reference samples?

APPLICATIONS OF (CERTIFIED) STANDARDS

Certified reference material serves multiple purposes in a laboratory.

- Method validation and revalidation, for example, to validate a method's accuracy, linearity, limit of detection, and limit of quantitation.
- To demonstrate equivalency of a method developed in-house with a standard method.

- To transfer analytical methods to other laboratories. Correct results with reference standards prove correct functioning in the new environment.
- To calibrate equipment when the final determinations are based on the measurement of a signal that must be correlated with the concentration of the analyte in the unknown sample. Examples are chromatographic and spectrometric equipment.
- OQ of analytical equipment, for example, to check the wavelength accuracy or linearity of a UV detector.
- To control the overall performance of an analytical procedure, for example, when using QC samples.
- To check the proficiency of a new person in the lab. Successfully running a reference sample proves the person's qualification to run this type of analysis.
- Interlaboratory tests to assess either the performance of a method or the proficiency of a laboratory.

TYPES OF MATERIAL AND DEFINITIONS

Different types of reference materials, certified reference materials, standard reference materials, and external and internal reference materials have been defined by ISO/IEC and the NBS (U.S. National Bureau of Standards).

Reference Material (RM):

A material or substance one or more properties of which are sufficiently well established to be used for the calibration of an apparatus, the assessment of measurement method, or for assigning values to materials (96).

Certified Reference Material (CRM):

A reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure, which establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence (96).

CRMs are referred to as Standard Reference Material (SRM) by the United States National Institute for Standards and technology. They are defined as follows:

Standard Reference Material

Certified reference materials (CRMs) issued under NIST trademark that are well characterized using state-of-the-art measurement methods for the determination of chemical composition and/or physical properties.

Reference materials or certified reference materials can be available as

- pure solutions for single component calibration,
- mixtures in solutions for multicomponent calibration, and
- solids with single or multiple components and a matrix as close as possible to the matrix of the unknown sample used as QC samples for long-term performance of a procedure.

REGULATORY AND QUALITY STANDARD REQUIREMENTS

Because of the importance of reference materials in laboratories, they are subject to the regulations and quality standards related to chemical laboratories. The main requirements are as follows:

- The need for (certified) standards and reference materials for calibration.
- Traceability to nationally or internationally recognized standards, wherever possible. If this is not possible, documented evidence about the standard's accuracy must be provided.
- Correct labeling with expiration date, storage conditions, date of receipt, and initial use.
- Qualification program for standards (tests to verify quality of incoming batches, e.g., identity and concentration, qualification program for suppliers).
- Prepared in accordance with written procedures.
- Prepared from chemicals of known purity and composition.
- Supplier certification to ISO 9001 or the equivalent.

Laboratories have to make the absolute comparison on the best effort possible. This can include the determination of absolute accuracy by an independent method or by comparisons with other laboratories.

TRACEABILITY TO NATIONAL OR OTHER WELL-CHARACTERIZED STANDARDS

A frequent question with any reference material is: How can I be sure that the concentrations written on the standard's label are correct? This important

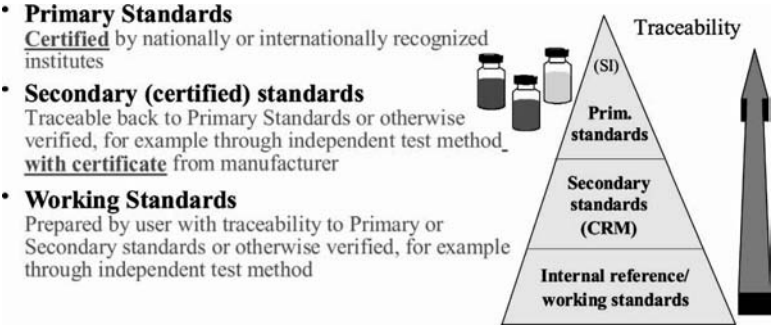


Figure 1 Traceability of working standards to secondary and primary standards. *Abbreviations*: CRM, certified reference material; SI, international system of units.

question has been addressed by many committees when developing standards, regulations, and guidelines for quality systems in testing laboratories. For example, ISO 17025 states:

> *Reference material shall, where possible, be traceable to SI units of measurement, or to certified reference materials. This also includes chemical standards.*

Figure 1 shows the traceability concept to primary standards that are nationally or internationally recognized standards. Physical standards are traceable to SI units: meter (m) for length, kilogram (kg) for mass, second (s) for time, ampere (A) for electric current, and Kelvin (K) for temperature. In contrast to physical standards in practice, there is no traceability to an SI unit for the Mol (10^{-23}).

For chemical measurement, national primary standards are prepared and certified under the inspection, supervision, or technical guidance of national institutes, for example, NIST in the United States or NITE in Japan.

Pan (97) suggested a classification scheme of reference material used for chemical measurements. The classification as described in Table 1 is well accepted in chemical laboratories.

The certified property value, or true value, e.g., concentration, of primary standards together with its accuracy are determined and verified by multiple laboratories using alternative methods. Stability and homogeneity are also determined.

Limited quantities of these primary standards are available, and suppliers of commercially available standards make a direct comparison with their own prepared standards. The comparison must be made in an accredited laboratory using validated reference methods. Suppliers offer these certified standards together with certificates that list the method, the concentrations,

Table 1 Characteristics of Reference Standards for Chemical Measurement

Primary reference material

- Also called primary standards
- Developed by a national metrology laboratory
- Certified by primary method
- Recognized by a national decision
- Traced back to SI units and/or verified by international comparison

Certified reference material

- Also called secondary standards
- Derived from primary reference material with statement of uncertainty
- Usually prepared by a national or otherwise specialized reference laboratory
- Certified by reference methods or comparison methods
- Recognized by national or otherwise specialized authoritative organization

Working reference material

- Also called internal reference material
- Derived from certified reference material
- Accuracy verified by well-characterized and validated methods

the uncertainty, and the national standard committee that was responsible for the certified standard.

Laboratories that purchase certified reference standards can use these standards directly for instrument calibration. They also can use them to prepare homemade internal reference standards, which then are used to prepare working standards for day-to-day use.

REQUIREMENTS FOR (CERTIFIED) REFERENCE MATERIAL

Because of the importance of (certified) reference materials in the analytical process for data accuracy, laboratories should ensure that the material meets the following requirements:

- The compounds and concentration should be as similar as possible to the unknown sample.
- The material should be "matrix matched." The matrix of the reference sample should be similar to the matrix of the unknown sample. The same source of error should be encountered when analyzing certified reference materials and unknown samples. For example, if the analysis includes a step where the analyte is extracted from the matrix (e.g., polynuclear aromatic hydrocarbons from a soil sample), the

accuracy determination must demonstrate that no or a well-known analyte loss occurs during extraction. If there is one, the amount of loss must be correctly determined for the calibration. Unfortunately, full matrix matching frequently is an unrealistic requirement. There are hundreds of thousands of chemicals being analyzed in all types of matrices, but there are only tens of thousands of certified reference materials available.

- The reference material should be homogeneous. Portions of the material will be used from different locations in the container at the same or at different times. Homogeneity ensures that all material at different locations is the same. The difference between sample measurements from different locations should be smaller than the overall uncertainty limits. The material should be checked for homogeneity as part of the verification process.
- If there is a risk of segregation during transport or storage, the material must be rehomogenized before use. Information on rehomogenization should be available from the supplier.
- The certified properties of the reference material and the matrix should be stable. Portions of the material will be used from the container at different times. Stability ensures that all material at different times is the same. The material should be checked for stability as part of the verification process.
- The uncertainty of the value should be estimated for certified reference materials.
- The procedure for characterizing the reference material should be validated, the limits should be known, and the method should be fully documented and available to the user of the material. Reference materials are certified according to recommendations in ISO/IEC Guide 35 (16).

PREPARATION AND TESTING OF (CERTIFIED) REFERENCE MATERIAL

The preparation and certification of reference materials should follow documented procedures in a quality standard environment. ISO Guide 35 (16) gives several technically valid approaches for certifying this material. For a certification, there are essentially three approaches:

- *Definitive method:* The method must be based on first principles and have very high precision and essentially zero systematic error.

An example is the use of isotope dilution mass spectrometry for the characteristics of trace level elements in natural matrix elements. The certification is done in a single laboratory.

- *Independent measurement method:* Two or more reliable independent methods are used. The method must be proven to give accurate results. The certification is done in a single laboratory.
- *Interlaboratory consensus method:* A number of laboratories analyze in replicate one or more units of the material being characterized. The participating laboratories may choose their own method or all laboratories may use the same method. The consensus value is usually taken as the mean.

PREPARATION OF "HOMEMADE" REFERENCE MATERIAL

Certified reference standards are quite expensive and frequently unavailable for a laboratory's task. To save costs, it is recommended to prepare reference standards as working standards, also called laboratory standard materials or internal reference materials, in laboratories for daily use, and to calibrate these standards using the certified standards. In this way, the certified standards will last for a long time. Special care must be taken when comparing the working standard with the certified reference material. The method used for the comparison should be validated, and the measurement uncertainty well known. It is a good practice to analyze and characterize the working standard in more than one laboratory, or, if this is not possible, at least within one laboratory by several operators on different instruments over several days to eliminate environmental effects.

Preparing Working Standards and Internal Reference Material from Certified Reference Material

When preparing internal reference material from certified reference material, the following steps are recommended:

- Develop a procedure for preparing the internal reference material and follow the procedure.
- The composition of the internal reference material should be as close as possible to that of the samples.
- Use pure material; if possible, use a primary standard with traceability to a nationally recognized standard.

- Prepare sufficiently large quantities. The quantity depends on the frequency of use, on the amount used per session, and on the stability. For solid materials, 1–10 kg is appropriate if the material is used frequently (1–10 L for liquids). More material should be prepared for reference materials that are used among different laboratories.
- Homogenize solid material.
- Stabilize the material. Most materials change in time due to evaporation or chemical reactions initiated by temperature, light, air, or humidity. The values to be certified may, therefore, change. To stabilize the material, it is usually dried either by oven drying or freeze-drying. The stability should be verified with accelerated normal laboratory conditions. Based on such studies, the material should be labeled with an expiration date.
- Verify accuracy through comparison with a certified reference material or through comparison with other independent methods.
- Verify the accuracy in a second laboratory.
- Provide information regarding shelf life, storage conditions, applicability, safety precautions, and restriction of use.
- Label the working standard with the date of expiration.
- Document the person who prepared the standard and the date when it was prepared.
- Document all details of homogeneity trials, stability trials, and the method used for qualification.
- Estimate, document, and report an estimate of the uncertainty in the certificate.

CORRECT USE OF CERTIFIED REFERENCE MATERIAL

The user of certified reference materials should be familiar with all information pertinent to the use of the certified reference material as specified by in-house or external producers. Particularly important are the

- intended purpose in a laboratory,
- period of validity before and after its first use,
- storage conditions,
- instructions for use,
- specifications for validity of the certified properties, and
- information on uncertainty.

QUALITY ASSURANCE PROGRAM

Each laboratory should have a QA program for reference materials and standards, which should be part of the company's or laboratory's quality plan. Steps in this program can include the following procedures:

- Policy on when certified material is required.
- The qualification of the supplier. Certification of ISO 9001 or an equivalent standard is strongly recommended; otherwise, a direct audit is recommended.
- Frequency and types of checks of incoming material. Checks can include verification of identity and amounts.
- Registration of the material in a database.
- Handling and storage of the material.
- Preparation of internal reference material and working standards from purchased material.
- Labeling, e.g., expiration date, storage conditions, and toxicity.
- Regular checks of the material, e.g., for purity and stability.
- Reference materials, primary, working standards, and certified reference materials should be subjected to periodical intermediate checks using a defined procedure.
- Actions to be taken in case the acceptance criteria are not met.
- Incoming tests when the reference material has been prepared and delivered from another laboratory in the same company (this also requires some checks).
- Disposal of used material.

Summary Recommendations

- Develop a policy and procedures for (certified) reference materials. (When is which quality of material required? Which type of traceability is required?)
- Develop procedure for qualification of (certified) reference materials and suppliers.
- Develop procedures for preparing homemade reference and working standards.
- Purchase certified reference materials (if available), and prepare relatively large amounts of in-house reference and working standards.
- Develop a QA program for (certified) reference materials.

15

People

What Is Discussed in this Chapter?

1. FDA and ISO 17025 requirements
2. The key issues when recruiting new people
3. How to develop a training program
4. How to qualify people for their jobs
5. The training methods available
6. How to document evidence of successful qualification

The single most influential factor in acquiring accurate and reliable data is the hiring, training, and managing of qualified people. Regardless of all the documentation and automation available in a laboratory, if people are not properly qualified and motivated to handle all laboratory activities, one will not obtain consistently good analytical data. For example, the best computerized systems cannot generate accurate and reliable data if the operator makes wrong entries because he or she did not receive sufficient, job-oriented training. In order to perform the job well, each employee must have a background combining education, experience, and training.

REGULATIONS AND QUALITY STANDARDS

Because of the importance of the people factor, all quality standards and GxP regulations have chapters on people qualification and training. The following

sections list the training related paragraphs of the most important FDA GxP regulations and of ISO 17025:

21 CFR Part 211 (211.25)

Each person engaged in the manufacture, processing . . . of a drug product shall have education, training, and experience, or any combination thereof, to enable that person to perform the assigned functions. Training shall be in the particular operations that the employee performs and in current good manufacturing practice . . . as they relate to the employee's functions. Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.(1)

21 CFR Part 58 (58.29)

Each individual engaged in the conduct of or responsible for the supervision of a nonclinical laboratory study shall have education, training, and experience, or combination thereof, to enable that individual to perform the assigned functions. Each testing facility shall maintain a current summary of training and experience and job description for each individual engaged in or supervising the conduct of a nonclinical laboratory study.(32)

21 CFR Part 820 (820.25)

Each manufacturer shall establish procedures for identifying training needs and ensure that all personnel are trained to adequately perform their assigned responsibilities. Training shall be documented. (107)

21 CFR Part 11 [11.10 (i)]

Determine that persons who develop, maintain, or use electronic record/electronic signature systems have the education, training, and experience to perform their assigned tasks. (42)

ISO/IEC 17025 (5.2)

The laboratory management shall ensure the competence of all who operate specific equipment, perform tests and/or calibrations, evaluate results, and sign test reports and calibration certificates. When using staff who are undergoing training, appropriate supervision shall be provided. Personnel performing specific tasks shall be qualified on the basis of appropriate education, training, experience and/or demonstrated skills, as required.

The management of the laboratory shall formulate the goals with respect to the education, training and skills of the laboratory. The laboratory shall have a policy and procedures for identifying training needs and providing training on personnel. The training programme shall be relevant to the present and anticipated tasks of the laboratory. The effectiveness of the training actions taken shall be evaluated. The laboratory shall maintain current job descriptions for managed, technical and key support personnel involved in tests and calibrations. (53)

ISO 17025 is most specific and gives good recommendations, which can also be used for FDA and international GxP environments.

The list below summarizes regulatory requirements and recommendations based on common sense:

- People should be qualified for the job (education, experience, training). Training should enable the performing of assigned tasks.
- Everybody should be trained (including part time employees, temps, all management levels).
- Training should cover operational tasks, GxP, and quality systems.
- A company's training program should be described in policy documents, in a master plan, or in the company's quality plan.
- There should be a procedure on how to train individual employees and QA should verify that procedures are followed. This includes identifying training needs by comparing existing with required qualifications.
- The efficiency of trainings should be assessed. This includes verification that training contents have been well received and understood.

- Training should be delivered by qualified trainers. The qualification of the company providing the training and/or the trainer should be documented.
- Training should be documented for each employee. Companies should maintain a summary of job descriptions, education, experience, and trainings. This also includes IT professionals and software engineers.
- Training should be an ongoing effort.
- Training should be part of regular quality audits to verify that training programs and procedures for trainings are followed. This also includes verification that templates and checklists that are part of the procedure are used adequately.

The words "adequately" and "sufficient" are mentioned in most regulations and in some of the warning letters. The preamble of 21 CFR 820 has a statement on this: ... *The manufacturer must determine for itself what constitutes "sufficient" personnel with proper qualification in the first place* (107).

RECRUITING QUALIFIED PEOPLE

It is well beyond the scope of this book to teach managers how and where to recruit people. Most organizations have reasonably well-structured qualification requirements and well-established hiring processes. However, because this is such an important topic, readers should at least consider the following four recommendations:

1. When recruiting new people for a specific job, it is very important that the person has the right knowledge and technical qualification for the specified job, as well as the right personality to fit into the laboratory's environment. The technical skills may have been obtained through education, and/or experience in a specific job. These are well-known criteria usually used for hiring new people. However, in today's rapidly changing world with changing working tools, it is equally important that the person have proven flexibility to learn new techniques, processes, and tools and to take over new tasks. For example, being willing and able to work with modern online communication media like the internet and the intranet is very important, even for those jobs that currently do not require such knowledge.

2. Teamwork is becoming more and more important. With globalization, tasks are shared not only within a single laboratory but within a company across divisions, countries, and continents. Frequently, part of the work is outsourced to other companies, and processes are improved through working closely together with suppliers and customers, all of which requires excellent communication. Therefore, evidence of good teamwork and communication skills is of utmost importance.
3. Hire people who love to do the work they are supposed to do. Make sure they are enthusiastic about working in an analytical laboratory. This natural motivation can be assessed during interviews and when the candidate(s) is giving a presentation on his or her previous work.
4. One should always consider the subsequent step in respect of the candidate's next possible job or career plan. It is very unlikely that somebody will remain in the same job forever. If the candidate may have to take over supervisory responsibility, relevant criteria should also be applied when interviewing for a job that does not have supervisory responsibility.

The typical process for hiring new people is as follows:

- Description of the job, including its "must-have" and "want" requirements
- Job posting, internal and external
- Screening of applications
- First round interview
- Second round interview
- Generating and signing the contract

Searching for Candidates

Finding ideal candidates can be very difficult for certain specialized jobs. All types of sources should be used, such as the following:

- Internal job boards
- Posting in company internal newspapers and the intranet
- Posting in external newspapers, magazines, and the internet (electronic bulletins)
- Posting at schools, universities, and institutes

- Using state employment services (unemployment office)
- Using private employment agencies (search companies). These can be very effective and may work well when looking for people with specialized skills. The employer describes in great detail the job position and "must-have" requirements. The agencies contact candidates and ask them if they are interested in the job. Usually, the search company charges a fee of up to 30 percent of the annual salary if the hiring is successful.
- Advice from company internal and external colleagues
- Posting at symposia and exhibitions

Most people get their jobs using informal methods. This may be through networking with people you know and by contacting the candidate directly, or through his or her supervisor, if the person is from your own company. If you have to hire people more frequently, develop and maintain a list of contacts who you may ask if need arises. Also, keep a list of candidates whom you should regularly contact and talk to about their interest in working for your department. In this way, you can watch their ongoing performance; when you really have a job opening, the hiring process is then quite rapid. You should use all types of resources to develop such lists: friends, colleagues from your own company and from outside your company, scientists you may meet at conferences or symposia, and even competitors whom you may meet at exhibitions.

Job Posting

Any job advertisements should have an attractive format and contain a clear indication on how to obtain further information and who to contact to make an appointment for an interview.

In general, any job posting should include the following:

- Description and location of your organization
- Title or summary description of the position
- Description of tasks and responsibilities
- "Must-have" and "want" requirements
- Contact person, phone number, and address

Screening of Applications

The first step in selecting possible candidates is the screening of written applications. It is recommended to use checklists with check items for the following:

- Is the documentation complete?
- Can any conclusions be drawn from the letter regarding personal style and how he or she may fit into the lab environment?
- Does the candidate meet the "must-have" requirements?
- Which "want" requirements are met?
- Is there any indication of criteria such as work attitude, creativity, and communication capability that is beyond standard or average?

THE INTERVIEW

The interview is the most important step in the process and should be discussed in a little more detail. Some of the questions that should be answered before an interview takes place are as follows:

1. Who should participate in the interview(s)?
2. What questions should be asked at the interview(s)?
3. What conclusions can be drawn from the answers?

Recommended interview participants:

- First line supervisor
- At least one manager level above
- One or two colleagues of the supervisor
- One or more colleagues of the prospective new employee
- Member of personnel department

Including future colleagues of the candidate is important to ensure acceptance and a smooth integration in the laboratory. The number of interview candidates should be selected in such a way that the interview process does not last for more than one day. Before each interview starts, every interview participant should be well informed of the job description, the "must-have" and "want" requirements and the candidate's background. Interviewers should get a good idea of the candidate's technical background as well as some personal characteristics. For example, from the average time spent at one particular company and in one specific job, one can draw conclusions about the willingness to work at one company for a longer period of time or the candidate's flexibility to take over new responsibilities. The lead interviewer, usually either the direct supervisor or the representative of the personnel department, should talk individually with each interviewer and provide some recommendations on what each person should cover as a minimum. This will avoid redundancy of questions and increase the amount of information interviewers receive. However, on certain critical issues, it may be valuable for the same questions to be put to the applicant by different interviewers.

Every interview situation is so different that it is difficult to give general recommendations. Here are just a few considerations that an interviewer may wish to bear in mind. What one really wants to find out is how the candidate will perform in the future. As the future is very difficult to predict, the most accurate information can be obtained from the candidate's behavior in similar situations in the past. Therefore, most questions should be related to how the candidate worked to solve specific problems in the past. For example, if you are looking for a creative person, ask the candidates to provide relevant examples from their work in previous positions. Similar questions should be asked on flexibility, self-motivation, problem-solving skills, work ethic, broad interests, supervision (if this is a "must-have" or "want" requirement), and broad personal skills. If a candidate claims to have specific skills, always ask for examples or references.

The overall key success factor of an interview is to ask specific questions and get candidates to talk about their skills, experiences, work habits, and professional attitudes. A good rule of thumb is that during the interview you should talk for about 20 percent of the time and the candidate should talk for about 80 percent. A good way to encourage the applicant to speak is to ask open-ended questions beginning with "why," "how," and sometimes "what." These cannot be easily responded to with a simple "yes" or "no." There may be follow-up questions to specific important topics, such as, "Tell me more about . . . ."

Besides the questions regarding technical qualifications, answers should be obtained to questions relating to personal skills such as

- flexibility,
- ability to learn,
- ability to take risks,
- ability to deal with problems,
- ability to work in a team,
- ability to listen,
- creativity,
- ability to meet critical time schedules,
- verbal and written communication skills, and
- work attitude.

Typical questions for the candidate are as follows:

- Why did you apply to our company?
- What do you know about our company?
- Why did you apply for this job? What is attractive and what is not?

- What are your qualifications for this job? Give examples to prove your statements.
- What do you like or not like about your existing job?
- What work style do you prefer? Would you prefer to work independently or with clear guidelines?
- Would you rather work with others or alone?
- What would be your ideal work group?
- Have you ever had to motivate coworkers? Describe how you did this.
- What form of communication do you prefer and why?
- Have you worked on major projects in any of your current or previous jobs? What were your contributions to the project?
- How many projects can you handle at one time? Give examples.
- What is your added value to the new job? What can you do that others cannot? Give examples for your statements.
- What are your strong points? What are your weaknesses?
- What is your learning style (self-study, classroom trainings, on-line)?
- How do you keep informed professionally?
- What important trends do you see in our industry?
- What do you think about your current/former supervisor?
- What is your definition of success? How would you describe success?
- How do you make decisions? Describe the process you go through to make decisions.
- What is your motivation to change your job?
- Why should we hire you?
- Do you have any examples that prove your creativity?
- Describe a situation from your current/previous job where you experienced and solved a serious problem.
- What are things you find easy to do?
- What are the things you find difficult to do?
- What kinds of decisions are most difficult for you?
- Have you ever had to work under pressure and deal with deadlines?
- How do you deal with unexpected events in your job?
- Under which circumstances would you work overtime and on weekends?
- How long would it take for you to make a contribution to our company?
- What do you think are the most important success factors for the new job?
- How long do you plan to stay in the new job, and what is your long-term goal (five years)?

- How would you rate your writing skills as opposed to your oral communication skills?
- What kinds of people do you like to work with?
- Do you prefer delegation or hands-on control? (The answer to this question will help to determine if the candidate will fit into your work environment.)
- What type of supervising would you prefer (detailed, independent)?
- You have been in your previous position an unusually long period of time—why is this so?
- You have changed jobs more frequently than usual—why is this so?
- What are your outside interests? Do you have any hobbies?

Answers to these questions can best be obtained by talking about current and previous work. The candidate should always be asked to give examples for any statement.

If an important task of the applicant will be to give presentations, the candidate should be asked to give a presentation in front of an audience. The topic of the presentation should be selected by the applicant, and the presentation should not last for more than 15 to 20 minutes, including questions and answers. The presentation style, the logic behind the presentation, the level of excitement, the way difficult questions are handled, and, last but not least, the ability to meet the time schedule are all important criteria for judging technical, personal, and oral communication skills. Such a presentation also has the advantage that more people than just the interview team can listen to the presentation and give input on the applicant's personality and qualification. In this way, future colleagues who will be in direct contact with the new employee can be included in the hiring process so that they too can feel good about the candidate.

After the interviews, all interviewing team members should meet to discuss the outcome. Everybody should give their overall impression and findings from the interview before the lead interviewer opens a discussion on the final selection.

DEFINING AND COMMUNICATING JOB DESCRIPTIONS, TASKS, RESPONSIBILITIES, AND DESIRED OUTCOME

Make sure that the job is accurately described and that tasks and responsibilities are well understood and accepted by the chosen person. This holds for both new and senior people. People may become very discouraged if they do their utmost to do an excellent job and later discover they did the wrong thing. A good job description with clear written expectations on the goals and standards is of utmost importance. Typically, responsibilities of staff in testing laboratories include

- performing tests and calibrations;
- planning of tests and calibrations and evaluation of results;
- development, validation, and modification of methods;
- professional judgment; and
- managerial duties.

Besides the business tasks that are usually included in the laboratory's objectives, each person should also propose and discuss with the supervisor some personal development goals for a given time frame. Because responsibilities and job tasks can change over time, these should be reviewed on a formal basis at specific time intervals.

Monitoring Progress and Providing Feedback

The person's development process in the job and the extent to which the previously specified objectives have been met should be monitored. Instant and regular feedback should be given to employees on how they are doing and how they could improve their performance. Usually, more formal performance reviews are done each year (Table 1). Evaluation items include quantity and quality of work, communication and teamwork, creativity, customer satisfaction, and work safety. Other items to be discussed include the employee's personal long-term goals and possible barriers preventing good performance. Many companies supply forms to be used for preparation and during the meeting itself and to document the results and objectives for the following year. It is important that there is consistency between the person's objectives and supervision on the employee's appraisal. If this cannot be achieved, other people could be invited to a future meeting (e.g., the next level manager or a member of the company's workers' council).

Regular feedback and performance evaluation meetings encourage a more positive attitude about the employee's job. The supervisor develops a better understanding of the employee's strengths and weaknesses and about training needs and career plans.

Continuous good work should be rewarded. Promotions or financial compensation are ways of doing this, but analysts may have other wishes: prestige among colleagues, visibility in a larger organization, and chances to learn new things. Frequently, people also want to share their success with their families.

TRAINING

Well-trained personnel are among a company's most valuable assets. Proper training not only builds skills as required for the job but also builds confidence. Training should go beyond analytical instrumentation and methods. It should

Table 1 Form for Joint Annual Review

Name	
Job title	
Department	
Date	
Main job duties and responsibilities (refer to job description and goals/measures from last year)	
Main achievements	
What did go well, what did not go well, why was this? **What was different from previous years?**	
Working relationships and performance	
Points that may be discussed Qualitative Quantitative Communication Work attitude Motivation Safety	
Summary of action plan	
What should be done differently in the future?	
Development goals, short term, long term	
Main goals/measures for next year	

also include safety and personal skills, such as improving creativity, communication, and teamwork. As a rule, training should account for 15 to 20 percent of an analyst's time. Initial and ongoing training should be given on

- analysis techniques;
- equipment;

- methods and procedures;
- regulations and quality standards;
- environmental, health, and safety;
- teamwork;
- improving communication; and
- improving creativity.

Unfortunately, training is traditionally the last item addressed by supervisors and the first cut when time or budgets run out. A high-quality people training system should be in place to ensure that

1. laboratory staff have sufficient entry training and permanent ongoing training to keep up-to-date with constantly changing instrument capabilities and regulatory and quality standard requirements, and
2. all education and training activities are documented.

A problem may occur with training if personnel are brought in on a short-term basis from another department. Such people may have adequate experience and knowledge for their permanent job but not for the one actually performed. It is important that there is documented evidence that the current job can be performed with sufficient quality. This is relatively easy to do if the job is similar. A statement about the similarity, together with a reference to the qualification documents in the other department, is sufficient. If the job is different, there should be full qualification documentation based on trainings for the new job.

Strategy for Training

To make trainings efficient and compliant with FDA regulations the following is required:

1. A commitment from corporate management towards qualification and training of employees.
2. A training master plan that describes how to ensure qualification of people.
3. A training plan for each employee
4. One or more SOPs on how to implement the training plan.

A company's commitment towards people qualification can be expressed in a policy statement that can be a stand-alone document or also part of a company's quality plan. Commitment from management is important because only this ensures getting the right resources so that trainings can be provided efficiently on an ongoing basis. Training budgets are typically the ones that are cut first as part of company's cost-saving program, especially when the trainings are provided by external resources and traveling costs are

Figure 1 Training master plan and individual training plans for employees.

involved. Without management commitment training plans cannot be implemented

FDA regulations specify what should be done but say nothing about how requirements should be met. This should be defined by individual companies. A good way to document the company's approach towards compliance is to develop a training master plan. From a training master plan training plans for individual employees can be developed.

Figure 1 shows the relationship between the master plan and individual plans and key contents of each document.

The training master plan should be endorsed and approved by the appropriate senior management. Review and familiarity of the overall training program and the master plan should be included in the normal staff training. The master plan should be periodically reviewed and updated, if necessary.

The training master plan documents the company's approach towards compliance. Such a plan is important to ensure consistent and efficient implementation of trainings. It can also be readily used to answer the inspector's questions, such as "What is your company's approach for training and people qualification?"

The plan should document

- Who is responsible
- What to train
- Who to train
- Options on how trainings should be conducted
- Timing of trainings
- Assessment of trainings
- Assessment of trainers
- Documentation of trainings

FREQUENCY OF UPDATES

21 CFR 211.25 (1) has a statement explaining that training is not a one-time effort but needs to be done on a continuous basis.

> *Training in current good manufacturing practice shall be conducted by qualified individuals on a continuing basis and with sufficient frequency to assure that employees remain familiar with CGMP requirements applicable to them.*

This statement is related to GMP training but it is also equally applicable to other trainings. Update trainings could be just a refresher or it could be for one-off or ongoing updates. For example, compliance training can include an update on recent FDA warning letters or other inspection findings. Updates on technical trainings could include an overview of recent conferences or scientific publications related to the topic. The FDA's expectations are that the ongoing training should ensure that the program and materials keep pace with job requirements and performance expectations throughout the entire employment. Update trainings are an absolute must when procedures have changed or when the person is assigned new tasks that require the knowledge of new SOPs. An example would be if a new instrument arrives from a different vendor and the employee has not received any training on this instrument.

The FDA is not specific about the frequency of updates. Ask two questions when defining the frequency: "How critical is the task being performed?" and "How complex is the task?" A critical and complex task performed every two or three weeks may require an annual training, but on the other hand a simple non-critical task performed every day will only require an update of the SOP changes. Guidelines and examples for frequency of updates should be documented in the company's training master plan. Individual training plans should include specific information on updates for each type of training. Once the frequency and schedule are defined in the plan it is of utmost importance to comply with the plan.

Table 2 Training Methods, Training Tools, Training Organizations

Training methods	• On the job • Individual instruction • Classroom training • Self-study
Training tools	• Paper • Audio • Video • Slides • Computer-based • Multi-media • Telephone • Intranet and Internet
Who delivers trainings	• In-house specialists • Instrument vendors • Scientific organizations • Private organizations (consultants) • Schools and universities

Methods of Training

There are different training methods for different circumstances and requirements. The methods, tools, and possible trainers are summarized in Table 2, and the methods are discussed in more detail below.

Classroom Training

Classroom training occurs in traditional seminars that are offered by instrument vendors, consulting companies, and technical organizations. The advantage is that a large number of people can be reached at one time, and direct feedback comes from the attendees in the form of questions that can be answered directly by the instructor. In addition, students can share their experience with others. The disadvantage is that such training courses may not be scheduled when required.

Individual and Small Tutorial Group Training

Small group trainings are offered by instrument vendors and consulting companies. They can be tailored to the knowledge and special requirements of the student. They can be scheduled at a time when the instruction is needed. The students' questions can be answered immediately by the instructor. The disadvantage is that they are usually quite expensive.

Computer-Based Trainings and On-line Tutorials

Tutorials or computer-based trainings are programs that are part of the software and are relatively inexpensive. They are tailored to the specific training needs for the software. Interactive operation makes them highly efficient. They can be used as the operator progresses on the software. The disadvantage is that there is no direct feedback to the instructors or immediate answers from the instructors if there are any questions.

Videotapes

Videotapes are supplied with or are otherwise available for some software packages. The advantage over slides/audio is that moving pictures can better illustrate complex technical processes. The disadvantage is that video recorders are not usually readily available in offices and not enough videos are available to demonstrate the tasks for which they would be most useful, e.g., complex technical processes.

Multimedia on CD/DVD

Text, audio, and video pictures make CD/DVDs ideal to convey all kinds of information: analysis techniques, complex technical processes, as well as instrument operation. The disadvantage is that they are expensive to produce and not many such tools are available for topics related to this book.

Standard Operating Procedures

SOPs can be a useful training tool for operating and maintaining an instrument. Typical step-by-step instructions make it easy to learn the instrument functions. There are usually no additional costs for the acquisition or development of training material because the SOPs should already exist. The disadvantage is that they provide no opportunity for personal interaction.

Textbooks

Textbooks are traditional, self-paced training tools. They are relatively inexpensive and are most convenient because they are easily transported and readily available when and where they are needed. They are useful for obtaining information on regulatory and quality standard compliance. They are also a useful source for reference material and checklists. The disadvantage is that they provide no opportunity for personal interaction, and complex processes are difficult to communicate.

On-the-Job Training

Learning by doing sometimes appears to be least costly, but it also requires good supervision. Execution should be planned in as much detail as classroom trainings. On-the-job training is not appropriate for new technologies.

Web Seminars

An increasing number of companies provide on-line trainings over the internet. The presenter sits somewhere in an office and speaks into a telephone. He/she moves the slides and the audience watches the slides on a computer screen and listens to a presentation on the phone. Some of the presentations are interactive, which means the students can ask questions either through a chat room or over the phone. An advantage is that there are no traveling costs involved and students still have access to well-known presenters. A disadvantage is missing face-to-face interaction between the presenter and the trainee.

Teleseminars or Audio Seminars

These are similar to web seminars. The difference is that the presentation material is typically sent by e-mail or uploaded to a website prior to the seminar. During the seminar attendees can watch the slides and listen to the presenter over the phone. Interaction is through the phone. An advantage is that there is no need for on-line internet connection during the presentation. One can attend the seminar from wherever a phone is available. Some companies also record the seminar on a CD and make it available afterwards. This is useful if trainees cannot attend the live training sessions.

Web seminars and audio seminars are quite useful for updates on specific topics, e.g., when the FDA releases a new guidance. Such training is useful for global companies. It allows receiving the same new information at the same time at different sites. Some service providers also record the seminars and make them available on CD/DVD or via download from access-protected websites. (For an example, see 81.)

The Ideal Training Tool

The ideal training tool depends on the type of training task, on the availability of different trainings in the user's geographic area, and on the urgency of the training. A combination of different trainings, for example, with books or videos as pre-study material, followed by classroom trainings, is most practical.

Documentation of Trainings

Each training activity should be documented with content, dates, and location. An example for a template is shown in Figure 1. Documented training activities should include on-the-job training; individual instructions on specific tasks; official classroom trainings; short courses by scientific organizations; training on special techniques and instruments by instrument vendors; and self-study training by reading books, video trainings, or multimedia trainings.

Frequently asked questions are as follows:

- How should the success of a training be evaluated and documented?
- Where can I obtain certification of the quality of the training organization and the instructor? Who finally qualifies the trainer? What documented qualification should a training organization have?
- Which training activities regarding length should be documented: hours, half day, full day, a week?
- Is self-study appropriate? How should it be documented?

For all trainings, certificates on the successful participation should be available and signed by the instructor. Training certificates are often included in distributed material and provided at the beginning of the training. This is not appropriate and does not prove that the person participated in the full training. Certificates should be distributed at the end of the training, preferably after the attendees have successfully passed an exit test.

The training organization and the instructor should be able to demonstrate evidence of qualification. This may be via training records or other proof of competence, for example, a number of papers published or a number of presentations given on the topic where the speaker has been invited. The training organization should be ISO 9000-certified or should have documented evidence that follows another quality standard.

Some people learn best by reading books, watching videos, working through on-line tutorials, or using modern multimedia tools. The worry is how to document the success of these trainings. The author's recommendation for all self-study activities would be that the person's supervisor should sign off on the successful completion of these trainings. Supervisors are responsible for the qualification of their people. They should know the training needs and should be fully aware that successful trainings may be received in official training courses or through individual self-studies.

Regarding the documentation of trainings of different lengths, the author recommends documenting all training activities that last at least for two hours.

Besides documentation for training, it is recommended that for each job within a company, a file is kept with a clear job description and information on education and training requirements. It is also recommended that the company maintain an official personnel file for each employee that holds information on education, experience, ongoing training activities, and participation in proficiency testing programs. This file should be updated as necessary. Because this documentation should be available for internal and external inspectors, it is recommended to keep information on the job description, job requirements, skills, education, and training separate from other, more personal and confidential information, such as results of performance evaluations. Laws on privacy also often require that access to any personal file be restricted.

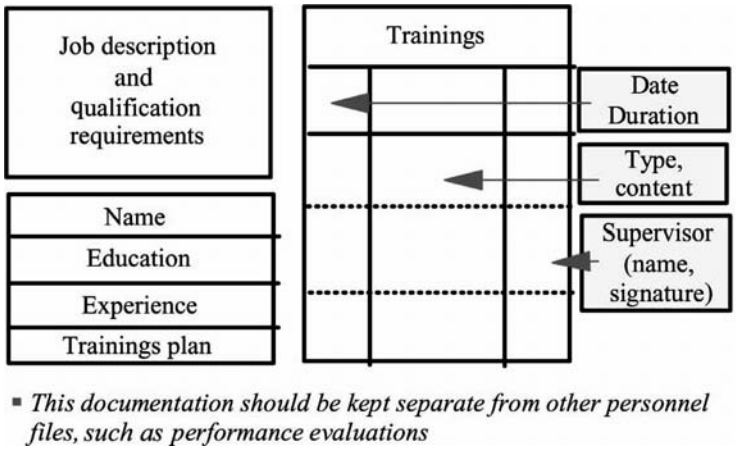


Figure 2 Form for job descriptions and training records.

Summary Recommendations

1. Allocate plenty of time for recruiting new people.
2. Develop an ongoing network of candidates among people you know.
3. Develop a policy and procedures for identifying training needs and providing training of personnel.
4. Describe job function and responsibility for each person.
5. Describe the person's education and experience related to the job function and responsibility.
6. Describe training requirements (gap between job requirements and current education or experience).
7. Develop a short- and long-term training plan for each person.
8. Document any training of personnel.
9. Review training needs every year.
10. Evaluate the success of the training.
11. Keep records of relevant competence, education, and experience of all personnel concerned with instrument qualification, sampling, measurement, data evaluation, and reporting.

16

Proficiency Testing for External Laboratory Qualification

What Is discussed in this chapter?

1. Operation of proficiency testing schemes
2. Advantages for laboratories
3. Evaluation procedures
4. Who should participate in proficiency testing
5. Frequency of testing
6. Limitations of proficiency testing

Proficiency testing by interlaboratory comparisons can serve two purposes:

1. Test an analytical method for effectiveness and ruggedness done on an irregular basis.
2. Assess the regular technical competence of participating laboratories to generate comparable analytical data.

This chapter focuses on the second item. Proficiency testing can enable a laboratory to compare its performance with that of other similar organizations and provide independent evidence of the validity and comparability of its data, i.e., to qualify the laboratory for specific analysis. Proficiency testing is complementary to the analysis of in-house QC samples. While QC analyses serve as a tool for internal QC, proficiency testing is a tool for external QC. Successful participation in proficiency testing schemes proves that the entire

Figure 1 Typical proficiency testing program.

analytical quality process is working well. This holds true for the analytical method, the equipment hardware and software, reference materials, and people. Bodies assessing the technical competence of testing laboratories, such as accreditation and certification bodies, use the results of proficiency testing in their assessment.

ISO/IEC Guide 43 Part 1 (99) has recommendations on the development and operation of proficiency testing. The second part covers guidance for selection and use of proficiency testing schemes by laboratory accreditation bodies (100). The Food Analysis Performance Assessment Scheme (FAPAS) has developed a detailed protocol for the analysis and organization of proficiency testing data (101,102).

PROCEDURE

In a typical proficiency testing scheme, portions of a well-characterized test material are distributed by the organizer, on a regular basis, to participating laboratories for analysis. The laboratories analyze the samples using methods and standards usually applied for that sample and send the results back to the organization that distributed the test material. Each laboratory's result is then compared to the true value for the test material concerned. Depending on the degree of agreement with the true value, the laboratories are scored and receive a report that enables them to review how well they have performed in the test. The results are confidential to the laboratory and the organizer, but clients of the laboratory and the accreditation body may request the test results. The process is illustrated in Figure 1.

Typically, calibration standards are not sent with the sample, and the analytical methods are not mandated. However, laboratories are advised to report the method because this may be used to obtain information if the method itself is a source of the deviation from the true results.

EVALUATION OF PROFICIENCY TESTING

The proficiency testing process should follow a protocol that has been developed by a collaboration of scientists from many countries under the joint organization of ISO, IUPAC, and AOAC International (103). One of the goals of the procedure is to find a way to convert the data of the laboratories into scores that are easy to understand and of universal applicability. The method recommended in the protocol, therefore, is based on simple statistics with no scaling. Each result (x) is converted into a "Z" score according to the equation:

$$z = (x - y)$$

where y is the assigned value, the best estimate of the true concentration of the analyte. Sigma (s) is the target value for the standard deviation of values of x. It describes the previously specified acceptable variability between laboratories and is related to the ruggedness of the analysis method. Z scores between $\pm 2s$ will occur in 95 percent of all cases and are regarded as satisfactory. Z scores between 2 and 3 are considered to be questionable and will occur in 5 percent of all cases, but those outside the range of $\pm 3s$ are considered unsatisfactory. Results are plotted to visualize them as easily as possible and are sent to each laboratory. An example is shown in Figure 2.

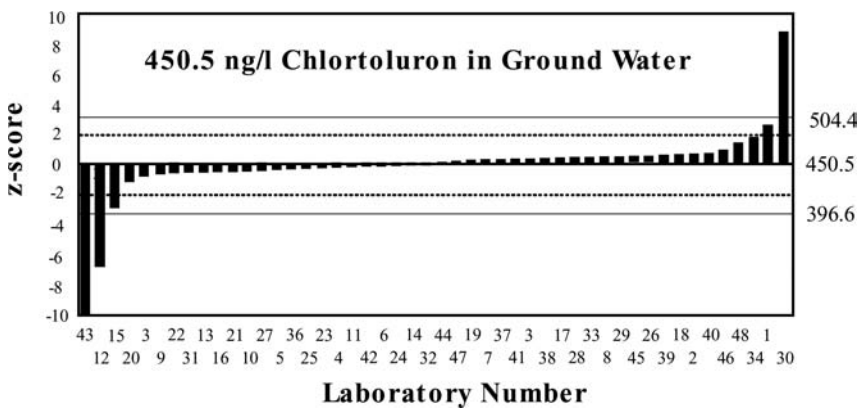


Figure 2 Plot of proficiency testing results. 44 laboratories are satisfactory, 3 would be unacceptable.

WHO SHOULD PARTICIPATE IN PROFICIENCY TESTING?

Proficiency testing is most appropriate for laboratories performing routine analysis of sample types that are also analyzed in other laboratories. Examples are environmental, clinical, and food testing laboratories where application specific proficiency testing schemes are frequently available. Proficiency testing is required by accreditation standards if proficiency schemes are available. Accreditation bodies encourage testing laboratories to participate in these programs as part of their quality system. A laboratory should look for organizers that use test samples that are the same or similar to typical samples analyzed in the laboratory.

FREQUENCY OF TESTS

An important parameter in proficiency testing is the frequency of testing. If done too frequently, costs for distributing the samples, performing the tests, and collecting and evaluating the data are too high. If done too seldom, a laboratory may not obtain feedback fast enough if there is a problem with analysis. One important criterion is to distribute the proficiency test results early enough prior to the next testing so that laboratories can react to the previous tests if there have been any problems. Once the system is established, one to three tests per year should be sufficient.

TESTING MATERIAL

A key element in the success of any proficiency testing program is the quality of the sample. This means the laboratory must obtain a sample with the true concentration at the time of the analysis. The variability between test samples delivered to laboratories must be less than the expected standard deviation for the test. This requires three steps:

1. The true concentration must be determined for the entire batch.
2. The batch must be divided into representative parts.
3. The sample must be stable under the conditions stored and shipped.

Some schemes use the mean value obtained from the participants to assign the true or consensus value. Such schemes will make laboratory results consistent, but not necessarily true. Ideally, assigned values should be defined by specialist laboratories using well-validated methods and material that can be traced back to national or international standards. The uncertainty of measurement should be minimized and under control.

ADVANTAGES FOR LABORATORIES

Participating in proficiency testing schemes can be quite expensive; therefore, laboratories should make a thorough judgment before deciding to participate. Advantages for a laboratory are as follows:

- External and independent assessment of data quality for specific tests.
- A means of demonstrating the data quality to customers, accreditation bodies, and regulatory agencies.
- A motivation to improve analytical quality.
- Information on the performance characteristics of analytical methods and the quality of reference materials.
- A laboratory experiencing difficulty with a particular analysis can often seek advice from the scheme organizer to improve its processes. Investigations can result in improved methods being introduced and, therefore, produce more accurate data.
- Compliance with accreditation standards.

PERFORMANCE IMPROVEMENTS

The main question is whether participation in proficiency testing will improve a laboratory's performance. Patey (101) reported a dramatic rise in the overall performance of laboratories after participating in proficiency tests. This observation was based on over 12,000 sets of results with 183 laboratories from more than 30 countries participating in the tests over 4 years. While at the outset only 60 percent of the laboratories sent in satisfactory data, this value has increased to 90 percent.

REMAINING ISSUES

Aside from all of the benefits for the laboratories, there are still some issues regarding proficiency testing:

- The quality of the results may not be representative for the laboratory. In order to look good, the laboratory may treat the proficiency sample differently from normal routine work. For example, multiple analyses may be done and average results reported, or only the most experienced operators and best instruments may be selected. Therefore, there is some doubt that the reported results are really useful to judge a laboratory's competence for the specific routine analysis.

- The proficiency sample is usually a real sample, not just a spiked standard. Because of a lack of knowledge as to the "true concentration" of the analytes, this may be determined by a consensus of laboratories that have determined the concentration. There is always a risk that this assigned result may not be correct. In this case, a high score will always make the laboratory results consistent but not necessarily true.
- The proficiency sample may not reflect the average concentration as distributed to other laboratories if errors have been made when dividing the sample.
- There are not enough organizers.
- Frequently, it is difficult to find the right sample that corresponds to a laboratory's competence.
- A good performance with a specific type of analysis does not necessarily indicate a good performance on other analyses. It is not always possible to distribute test materials that exactly resemble a laboratory's routine test samples.
- Proficiency testing schemes are relatively expensive, in terms of both organizational costs and the time spent by participating laboratories. Especially for small laboratories with a low sample throughput for a particular analysis, the costs are relatively high compared to the revenue from that specific analysis.
- Most proficiency tests are done on a more local basis with less international focus and with a relatively small number of laboratories. The real value of a specific scheme would be to demonstrate international comparability.

Summary Recommendations

1. Evaluate the need for proficiency testing.
2. Select the right proficiency testing scheme.
3. Decide on frequency of tests (consult accreditation body and organizer).
4. Evaluate your performance in comparison to others.
5. Discuss results and possible improvements with the organizer.

17

Audits

What Is discussed in this chapter?

1. Objectives of audits
2. Mistakes others made
3. Organization of audits
4. Differences between horizontal and vertical audits
5. Aspects to consider in preparation for an audit
6. How to conduct an audit
7. What should be included in an audit report
8. How to follow up audits

Audits are a key element of any quality system. Their objective is to evaluate activities and existing documentation to check whether these meet predetermined internal and/or external standards and/or regulations or customer requirements. There are several types of audits:

1. *Internal audits* are conducted on a regular basis to check whether particular departments and individuals adhere to company policies, standards, and procedures. These are a requirement of most regulations and accreditation standards relating to analytical laboratories.
2. In *second-party audits,* a purchasing company audits the supplier. These are commonly used to check whether a supplier meets the purchaser's requirements.
3. *Third-party laboratory audits* are used to ascertain whether a company or laboratory complies with national or international quality standards, such as the ISO 9000 and ISO 17025, or to check whether the company is competent enough to perform analyses, as specified in contracts with clients. Regulatory agencies inspect laboratories to confirm their compliance with GLP, GCP, and GMP regulations.

Besides checking compliance with internal and external standards, there is a second and even more important aspect of internal and external audits: They can be used to help improve processes and to establish a better system for the benefit of laboratory owners, employees, and customers. If the procedure is done correctly, laboratory departments can learn extensively from auditors and inspectors because, as outsiders, they may contribute useful expertise and tips on how to improve certain quality aspects. Laboratories may also benefit from the mistakes made by other laboratories. For example, the FDA documents deviations found during inspections as warning letters and regularly publishes them on the Internet (90). Extracts of GxP-related warning letters are also published on the internet (104). Occasionally, U.S. FDA and other inspectors give a summary of their findings at validation conferences (105,106).

Valuable resources in preparation for GxP-related laboratory audits are the laboratory inspection guides from the FDA (22) and PIC/S (19,20).

Before various audit techniques and audit items are discussed, some observations and findings taken from laboratory audits will be examined.

OBSERVATIONS REPORTED DURING INSPECTIONS AND AUDITS

Observations, as reported by inspectors or published by the FDA on the Internet, can be a useful source of preparatory information for laboratories. They may also help to improve a laboratory's work, as they enable the laboratory to take note of and avoid the same mistakes and, therefore, to implement their own processes in a better way. Table 1 includes a summary of audit/inspection findings.

The observations have been derived from a variety of sources:

- presentations given by inspectors (105,106),
- FDA Deviation Reports, e.g., Warning Letters or 483 form inspectional observations (90,104), and
- the author's own experience.

Observations listed here are considered to be representative within their categories.

PLANNING AND IMPLEMENTATION OF INTERNAL AUDITS

Needless to say, not all laboratories can be audited for all items at once. Over a certain period of time, however, all items should be checked in all laboratories. Therefore, audits should be conducted according to a long-term plan. The

(Text continues on page 221)

Table 1 Problems Found during Laboratory Audits

Procedures

- Written standard operating procedures were inaccurate, incomplete, and contained no documentation of origin, review, or approval.
- Failure to follow written production and process control procedures as required by 21CFR 211.100.

(Internal) Quality Audits

- Failure to conduct quality audits required by 21 CFR 820.22, and in your procedure QO02, "Audits" to assure your firm is operating in compliance with the regulations.
- Quality audits are inadequate to assure that the quality system is in compliance with the established quality system requirements and to determine the effectiveness of the quality system.
- We are requesting that you submit to this office, on the schedule below, certification by an outside expert consultant that he/she has conducted an audit of your establishment's manufacturing and quality assurance systems.
- Failure to document the dates and results of quality audits.

Personnel

- Failure to ensure that each person engaged in such activities has the education, training, and experience, or any combination thereof, to enable them to perform their assigned functions, as required by 21 CFR 211.25. Your failure to have staff adequate to perform their assigned functions is the number and type of inspectional during this inspection.
- Your firm fails to have sufficient personnel with the necessary training to assure that all activities required by (X) are correctly performed.
- Employee training on the use of the new [redacted] computer system, which is used in donor screening and product processing, was not complete.
- Your formalized training program is inadequate in that it does not address current Good Manufacturing Practices.
- There are no cGMP training SOPs in place and at least one employee denied knowledge of cGMP regulations.
- No one on the organizational chart, including supervisors in QA and QC, are identified as having academic or other suitable training in chemistry or microbiology
- A supervisor and QC manager could not explain how the calculation was done for the xxx assay determination

Laboratory Controls

- Your firm has no system for the receipt and storage of standards and analytical chemicals.
- Expired standards were used in the calibration of equipment. Working solutions were not properly labeled or documented in laboratory notebooks or other records in that the data did not bear complete information, including the analyst or preparer's identity, solution designation, strength, and expiry dates.

(*Continued*)

Table 1 Problems Found during Laboratory Audits (*Continued*)

- Failure to perform laboratory testing on each batch of drug product prior to release, to determine satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient.
- Extraneous HPLC peaks continuously explained to be auto injector contamination, no further investigation.

Laboratory Equipment Qualification

- The calibration procedure for HPLC systems is inadequate in that it did not include integrator and detector's linearity, injector's reproducibility, and accuracy of temperature settings for column heater and detector.
- Qualification and validation arrangements for the system were poor with a lack of formal protocols, acceptance criteria, testing procedures, records, reviews, error handling arrangements, formal reporting, and signing off
- Calibration records show many instances where examination of the pipettes found them Out-Of-Specification. There is no way to determine when the (pipettes) units in question have been in use for analytical purposes while Out-Of-Specification.
- Failure to ensure that all inspection, measuring, and test equipment is suitable for its intended purposes and is capable of producing valid results.
- Analytical balances are used outside specified range.
- You continued to utilize this revised QC Lab data acquisition system without ensuring that the system would perform as intended.

Computer/Software Validation

- Failure to have an adequate validation procedure for computerized spreadsheets used for in-process and finished product analytical calculations. SOP 644.00, QA/QC Spreadsheet Validation, is deficient in that only a small range of values are being used to challenge computerized spreadsheet mathematical calculations.
- Validation of the system did not include critical system tests such as volume, stress, performance, boundary, and compatibility.
- Firm lacks to validate computer data integrity. Also stress of the computer has not been tested prove that the system can run in parallel at the same time.
- The validation and installation records for the [redacted] computer system were incomplete.
- Complete diagrams and text descriptions identifying all other network program interfaces with XXX, and which specify the data being exchanged between the XXX and other programs have not been maintained or updated from original design specifications.

Vendor/Supplier/Service Provider Qualification

- The firm has no SOP for the qualification of vendors and contract laboratories, nor has such documented qualification been conducted.
- The firm has been using the service of ... for the testing of Purified Water; however, there has been no audit conducted at this contract laboratory.

(*Continued*)

Table 1 Problems Found during Laboratory Audits (*Continued*)

Methods and System Suitability Testing

- Linearity and limits of detection were determined above the limit of the test.
- Laboratory tests for assay, impurities, etc.were not performed according to established procedures described in the individual Drug Master Files (DMF) that specify the USP methods.
- Laboratory controls have not established that the test method for assay of xxx content of xxx "is scientifically sound to assure that this product conforms to specifications of strength, quality, and purity" (examples: insufficient separation, no verification of method suitability under actual conditions, etc.).
- There were no written procedures for the validation of analytical procedures and test methods. The suitability of such testing methods was not verified to ensure that they were compatible with conditions that exist in this facility (equipment, environment, personnel, etc.). Written procedures did not specify in-house limits for variable operating parameters that could affect accuracy, reliability, and reproducibility of test methods adopted from standard references and compendia.
- No reference in analytical method to recognized standard methods.
- Poorly controlled changes to test methods or acceptance criteria following failures.
- No reference in analytical method to recognized standard method.

Microbial Testing

- A total of ... microbial tests were conducted for this product, yet there was no documented investigation into these discrepancies nor was there any conclusion or follow-up.
- No microbial limits testing.
- No written procedures for any microbiological tests performed.

Stability Testing

- Failure to implement a written testing program designed to assess the stability characteristics of drug products, using reliable meaningful and specific test methods.
- One internal standard was four months old with no data on its stability over that period, in-process testing inadequately performed.

Out-of-Specifications – Failure Investigations

- Laboratory controls are deficient in that the firm established a written procedure, which allowed for the averaging of Out-of-Specification and within-specification analytical test data results.
- There are no documented investigations of process deviations or Out-of-Specification (OOS) laboratory results.
- The quality control unit lacks authority to fully investigate errors that have occurred.

(*Continued*)

Table 1 Problems Found during Laboratory Audits (*Continued*)

Corrective and Preventive Actions

- Failure to verify or validate corrective and preventive action to ensure that such action is effective and does not adversely affect the finished device.
- Failure to maintain adequate procedures for implementing Corrective and Preventive Actions (CAPA) such as analyzing data to identify existing and potential causes of nonconforming product or other quality problems.
- The response does not document that all other laboratory procedures have been reviewed for similar deficiencies.

Raw Data

- Laboratory records do not always include raw data for all the laboratory testing performed.
- Laboratory procedures are inadequate in that raw data was not always recorded.
- During the inspection of your facility, you were unable to present records of raw data pertaining to the subject stability batches submitted.

Records

- Failure to retain all production, control, or laboratory records to assure that drug products adhere to established specifications.
- Failure to maintain records of changes to documents.
- Failure to include in laboratory records complete records of the periodic calibration of laboratory instruments, and there are no calibration records available for the FTIR Spectroscope and the HPLC laboratory instruments.

Electronic Records

- In addition to the above listed violations, our investigator noted that the laboratory is using an electronic record system for processing and storage of data from the atomic absorption and HPLC instruments that is not set up to control the security and data integrity in that the system is not password controlled, there is no systematic back-up provision, and there is no audit trail of the system capabilities. The system does not appear to be designed and controlled in compliance with the requirements of 21 CFR Part 11, Electronic Records.
- Data files are automatically deleted after a hard copy is generated.

Documentation

- During the inspection, our investigator requested to see investigations of process deviations and Out-Of-Specification laboratory results. She was informed that these investigations are conducted but not documented.
- The response states that retrospective validation studies have been completed for all APIs and that protocols and final validation reports are attached. Only the Chinese versions were attached. We are unable to evaluate these studies at this time.

Source: Ref. 83.

Table 2 Horizontal Audit Schedule

Audit item	Q1	Q2	Q3	Q4
Quality system	x			
People qualification		x		
Facilities			x	
Procedures				x
Sampling		x		
Sample handling			x	
- - - - - - - - - - -				x
Others	x			

objective is that all departments or laboratories be audited for all items over the planned period. Priorities of the audits can also be set based on current trends and regulatory focus.

There are two ways to achieve comprehensive coverage—the horizontal and the vertical approach.

Horizontal Audits

Using the horizontal approach (Table 2), all departments are audited, in detail, for the same item at one particular time; for example, for organization and methods or equipment. In a subsequent audit, other items are checked. Horizontal audits may reveal only some of the weaknesses that may exist in the quality system.

Vertical Audits

In a vertical audit, all or a selected number of different items are checked at one particular time. In practice, not all laboratories are audited at the same time; they are audited according to an audit schedule (Table 3). In the author's experience, the horizontal audit scheme is preferable.

Table 3 Vertical Audit Schedule

	Q1	Q2	Q3	Q4
Lab 1	x			
Lab 2		x		
Lab 3			x	
Lab 4				x
Lab 5		x		

STEPS IN PREPARING AND CONDUCTING AN AUDIT

Below is a step-by-step recommendation on how to prepare and conduct an audit:

Preparation

1. Establish audit team and lead auditor.
2. List areas to be evaluated (see long-term plan, if any).
3. Review results of previous audits.
4. Contact laboratory.
5. Prepare an agenda.
6. Review agenda with laboratory and reach consensus.

Conduct

1. Review selected documents, e.g., procedures.
2. Opening discussion with management.
3. Review corrective actions from previous audits.
4. Review documentation: master plans, SOPs, test plans, sampling plans, training records, test results.
5. Walk through the facilities, observe laboratory work, and interview operators.
6. Examine test procedures and ask for some specific results. Trace the result back to methods for analysis and data evaluation to equipment, operators, and raw data. Review raw data. Verify if the equipment and data have been validated.
7. Give immediate advice if any noncompliance with standards has been found.

Conclusion, Report, and Follow-up

1. Have a closing meeting with all auditors and laboratory management.
2. The (chief) auditor/inspector summarizes all findings, assigns level of concerns to each finding, and listens to the lab's response. Any misunderstandings should be resolved at this point.
3. The (chief) auditor/inspector writes a summary report (the detailed report should not contain any surprises that were not mentioned in the summary). The chief auditor sends the report to laboratory management. This also includes a time frame when the response, e.g., 30 days, is required.
4. The laboratory resolves the problem and writes an official statement to the auditor.
5. If the statement is accepted by the audit team, the file is closed. Include the audit log that can be shown to external auditors/inspectors as proof for timely and successful audits.

AUDIT REPORT

After each audit, a report should be generated that includes

- auditor name(s);
- date of audit;
- areas audited;
- any noncompliance observed;
- categorization of the noncompliance (e.g., critical, serious, minor);
- corrective action agreed on, responsibility for corrective action, and its time frame for completion; and
- summary of audit findings, with positive statements, serious noncompliance, and recommendations for corrections and improvements.

A template for an audit summary report is shown in Table 4.

AUDIT CHECKLIST

For validation activities, including calibration and testing, special attention should be paid to maintenance and change control, safety procedures, backup and recovery, and error handling and recording. Table 5 lists possible audit items. Although there is some doubt about the usefulness of such checklists, they do, in fact, help to ensure that users have considered the most important requirements. The checklist should be used as guideline, but it is not all-inclusive.

Table 4 Problems Found during Laboratory Audits

Summary Audit Report
Date
Audit number
Auditor(s)
Location/Laboratory
Details of inspections (inspected documentation, equipment, raw data, etc.)
Observed non-conformities, with categories 1. critical 2. minor
Recommended corrective actions

Table 5 Audit Questions in Analytical Laboratories

Audit items	Questions
Management responsibility	• Is there a documented policy and commitment to quality? • Is there a chart of the organizational structure? • Are the responsibilities of each function defined? • Are there written protocols for a quality assurance program?
Facilities	• Is adequate space available for the type of testing performed? • Is the laboratory environment suitable for the work carried out?
Supplier assessment	• Is there a policy and procedure for purchasing equipment and chemicals? • Has the vendor been qualified? • Does the vendor have an established and maintained quality system? • For software vendors: Does the vendor provide evidence of validation during development? • For software vendors: can validation documents be made available? • For software vendors: can the source code of software be made available to regulatory agencies? (This question is only important for GLP/GMP compliance). • Is there an error tracking and response system for inadequate reports and enhancement requests?
Equipment	• Is there a list of all equipment used in the lab? • Are there functional and operational specifications for each piece of equipment? • Is there a protocol of installation qualification with test cases, acceptance criteria, and test results? • Is there a protocol of operational qualification with test cases, acceptance criteria, and test results? • Are (traceable) standards used for calibration and performance checks? • Are instruments calibrated/tested by qualified people? • Do test data sets for software qualification represent realistic data? • Have there been manual recalculations of selected critical software tasks?

(*Continued*)

Table 5 Audit Questions in Analytical Laboratories (*Continued*)

Audit items	Questions
	• Is there a preventive maintenance schedule? • Is there a schedule for ongoing calibrations and performance qualification? • Is there a record of on-system calibration, performance qualification and maintenance (log book)? • Are instruments labeled to indicate next operational qualification and/or calibration check date? • Are errors detected and recorded automatically by the system? • Are there documented procedures on error corrections? • Has defective equipment been removed from the lab or been labeled as 'out of service'? • Are there documented procedures for change controls? • Are test methods documented? • Has the scope of the method been specified (criteria, performance limits)? • For standard (compendial) and non-standard methods: Have these methods been validated for all performance criteria, as specified by the laboratory, and are the results documented? Has the suitability of such methods been verified to ensure that they are compatible with conditions that exist in the laboratory (equipment, environment, people)? • For nonstandard (noncompendial) methods: is there any documentation showing that these methods are equal to or better than standard (compendial) methods? • Does a protocol exist for the changes that would require a revalidation? • Are methods periodically qualified after the initial validation? • Have alterations to methods been authorized?
Chemicals and Reference material	• Are chemicals and reference materials labeled with content ID, date of acquisition/preparation, and the expiration date? • Are chemicals and reference materials appropriately stored? • If refrigeration is required below a specific temperature, is the temperature monitored?

(*Continued*)

Table 5 Audit Questions in Analytical Laboratories (*Continued*)

Audit items	Questions
	• Is the reference material certified and/or traceable back to national standards? • Is the (certified) reference material obtained with a certificate? • Does the certificate state the uncertainty? • If there is no traceability has the accuracy been otherwise verified? • Is the uncertainty of reference material known and has this been well-documented? • Has the supplier of (certified) reference material been qualified? • Is the shelf life of reference material known, how has it been checked and how is it documented? • Is the preparation of working standards and reagents documented?
Samples	• Is there a procedure for sample handling? • Is there a sample tracking system? • Are samples stored appropriately?
Documentation	• Is existing documentation (user manuals, on-line help, SOPs) adequate, complete, and up-to-date? • Is the documentation approved? • Does the documentation correspond to practice? • Is there an equipment log-book?
Data	• Is there an SOP for defining, collecting, entering, verifying, changing, and archiving (raw) data? • Is there a procedure for checking critical data? • Where control charts are used for quality control, has performance been maintained within acceptable criteria? • Is there a traceability of data to equipment and people? • Is there a way to track final data back to raw data? • Do inputs or changes to data include information on who entered them and, if they were changed, when and why?

(*Continued*)

Table 5 Audit Questions in Analytical Laboratories (*Continued*)

Audit items	Questions
Reporting	• Do reports provide adequate, complete and thorough information? • Have reports been dated and signed? • Do reports include information on the measurement uncertainty?
People	• Are there sufficient resources for timely response? • Are people adequately trained for their job? • Has the success of training courses been verified? • Are training records kept? • Is there an annual review of the training plan?
Internal audits	• Is there a documented procedure for inspections or audits? • Have regular internal audits been conducted?

Summary Recommendations

1. Develop a policy and procedure for audits.
2. Study FDA inspection observations.
3. Develop a schedule for internal horizontal and/or vertical audits.
4. Develop checklists and templates for conducting audits.
5. Learn from audits and improve your processes.

Appendix A

Glossary

A2LA	American Association for Laboratory Accreditation. A nonprofit, nongovernmental, public service, membership society dedicated to the formal recognition of competent laboratories and related activities. Accredits laboratories for compliance with A2LA's accreditation standards, which includes ISO 17025.
AAPS	American Association of Pharmaceutical Scientists
Acceptance criteria	The criteria a software product must meet to complete a test phase successfully or to achieve delivery requirements.
AU	Absorbance units
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.
AFNOR	Association Francaise de Normalisation. The French Institute for Standardization.
ANSI	American National Standards Institute. Official standards body representing the United States with the International Organization for Standardization.
AOAC	Association of Official Analytical Chemists. The primary objective of the AOAC is the development and publication of analytical methods for substances affecting public health and safety, economic protection of the consumer, or quality of environment.
API	Active Pharmaceutical Ingredients
AQC	Analytical Quality Control
Assay	To provide an exact result that allows an accurate statement on the content or potency of the analyte in a sample (ICH).
ASQ	American Society for Quality

ASTM American Society for Testing and Materials. A scientific and technical organization designated to develop standards on the characteristics and performance of materials, products, systems, and services.

Audit An activity to determine through investigation the adequacy of and adherence to established procedures, instructions, specifications, codes, standards, or other applicable contractual and licensing requirements and the effectiveness of implementation.

Audit tracking A procedural formality built into the operation of a system that ensures all interactions with the system are first authorized before being carried out and then recorded permanently in an operations log.

BCR Bureau Communautaire de Référénce. (Community Bureau of Reference), Commission of the European Community, that provides certified reference material.

British national formulary Guidance on prescribing and notes on drugs and preparations, published jointly by the British Medical Association and the Royal Pharmaceutical Society of Great Britain.

British Pharmacopoeia (BP) British Official compendium of monographs providing authoritative standards for the quality of many substances, preparations, and articles used in medicine and pharmacy. It incorporates monographs of the European Pharmacopoeia. It is a legally enforceable document throughout most of the Commonwealth and many other countries.

BSI British Standards Institution

Calibration 1) 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. Used by regulatory agencies to refer to the process of checking or adjusting instruments (including analytical instruments). Also used in chromatography to refer to the process of using standard samples as part of method verification.

2) An operational check that generally involves the use of standard materials or test instruments that have certification traceable to the National Institute of Standards and Technology (formerly the National Bureau of Standards).

Change control A procedural formality required for validation, defining how and when changes may be made and in which situations revalidation is required.

CE Capillary electrophoresis

CEN Comité Européen de Normalisation. The committee on European standardization. Its members are the national standards organizations of EC and EFTA countries.

CEN/CENELEC Comité Européen de Normalisation/Electrotechnical Standardization. The joint European Standards Institution.

Certified reference material (CRM) Reference material, accompanied by a certificate, one or more of whose property values are certified by a procedure that establishes its traceability to an accurate realization of the unit in which the property values are expressed, and for which each certified value is accompanied by an uncertainty at a stated level of confidence (ISO Guide 30:1992).

CITAC Co-operation on International Traceability in Analytical Chemistry. A forum for worldwide cooperation and collaboration on the mechanisms needed to ensure the validity and comparability of analytical data on a global basis.

Certification 1) Procedure by which a third party gives written assurance that a product, process or service conforms to specified requirements.
2) Documented review and approval of all qualification and validation documentation prior to release of the design production.
3) Documented review and approval process performed as the final step in a validation program to permit product release. 4) Requirement that each manufacturer of an electronic product certify that it conforms to all applicable standards.

cGMP Current Good Manufacturing Practice

Checksum Programming terminology for an arithmetic operation performed on the data immediately after being generated, the product of which is stored with the data. Future access to the data is subject to the same arithmetic check. Numerical matches confirm the data have not been tampered with, while mismatches draw attention to possible corruption of the data.

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 the U.S. Code and the companion regulations implementing the law are found in 21 CFR.

COMAR	Code d'Indexation des Matériaux de Référence. International database for registering reference material. Joint enterprise between the Laboratoire National d'Essais (Paris, France), the Bundesanstalt fuer Materialforschung und Pruefung (Berlin, Germany), and the National Physical Laboratory (Teddington, United Kingdom).
Compliance	A state of laboratory operations that ensures activities follow documented protocols. GLP compliance is the responsibility of the study director who oversees the facility, the personnel, the materials, and the equipment or subcontractors that fall under the compliance protocols. A particular instrument is only GLP compliant when validated and verified by the operator for the specific analysis to be performed. A vendor cannot claim GLP compliance for its products.
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.
Computer-related system	Computerized system plus its operating environment
Conformity	Fulfillment by a product, process, or service of specified requirements.
Control charts	Routine charting of data obtained from the analysis of standards or (certified) reference material to check that the results lie within predetermined limits.
CSVC	Computer System Validation Committee
DAB	Deutsches Arzneimittelbuch, German equivalent of the USP (United States Pharmacopeia).
DAD	(UV/visible) diode array detector (HPLC)
Data validation	A process used to determine if data are inaccurate, incomplete, or unreasonable. The process may include format checks, completeness, checks, check key tests, reasonableness checks, and limit checks.
Declaration of System Validation	An Agilent Technologies publication that testifies that the Analytical software products has been validated during its development and according to the Agilent Analytical Products Group Life Cycle.
Design Qualification (DQ)	Defines the functional and operational specifications of the instrument and details the conscious decisions in the selection of the supplier.

Design review Planned, scheduled, and documented audit of all pertinent aspects of the design that can affect performance, safety, or effectiveness.

Design specifications Description of the physical and functional requirements for an article. In its initial form, the design specification is a statement of functional requirements, with only general coverage of physical and test requirements. The design specification evolves through the research and development phase to reflect progressive refinements in performance, design, configuration, and test requirements.

DHSS Department of Health and Social Security. Former name of the British Health Authority, now the Department of Health.

EA European Co-operation for Accreditation. Merged in November 1997 from the European Accreditation of Certification (EAC) and European Co-operation for the Accreditation of Laboratories (EAL). A major role for the EA is to develop, evaluate, and ensure the maintenance of conformity assessment bodies. Membership in the EA consists of the nationally recognized accreditation bodies of the European Union and EFTA. Other non-EU/EFTA nations, with nationally recognized accreditation functions, in line with international standards, may also join as associate members.

EC European Community. See also EU.

EDQM European Department for the Quality of Medicines

EMEA European Agency for the Evaluation of Medicinal Products

EPA Environmental Protection Agency of the U.S. government. A regulatory body that develops and enforces all aspects of environmental monitoring, including the development of analytical methods.

Equipment Defined as the analytical measurement hardware including the firmware, for example, a gas chromatograph. In a computerized system, the equipment is controlled by the computer system. The computer system collects measurement data from the equipment.

Equipment Qualification (EQ) The overall process of ensuring that an instrument is appropriate for its intended use.

European Pharmacopeia Official compendium of the member states of the Council of Europe, which includes all EC and EFTA countries

EU European Union, formerly called European Community (EC) and European Economic Community (EEC).

EURACHEM EURACHEM: Established in 1989, provides a focus for analytical chemistry and quality related issues in Europe. Develops useful guidance documents for analytical chemists in the area of method validation and measurement uncertainty.

External audit Also known as a third-party audit. A periodic process carried out by an external body, to check that the laboratory's quality assurance system is effective, documented, and adhered to by all staff.

FAPAS The Food Analysis Performance Assessment Scheme

FDA Food and Drug Administration, a 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 United States.

FDA compliance policy guide FDA manual for FDA field operations personnel that contains policy guidance on FDA interpretations of regulations and other compliance policies.

FDA guidance documents Document published by U.S. Food and Drug Administration to provide drug sponsors with informal guidance on specific FDA requirements. Unlike regulations, guidelines are not legally binding. Alternative approaches can be used to implement specific requirements.

FDA inspectors technical guide Guide published by the Food and Drug Administration for its field inspectors. It is intended as a vehicle for making all FDA inspectors aware of selected technical information not previously available on a broad scale. Some of the topics addressed are lyophilization of parenterals, measurement of relative humidity in the ethylene oxide process, evaluation of production cleaning processes for electronic medical devices, bacterial endotoxins, new equipment static mixers, diathermy, and ethylene oxide sterilization.

Firmware The combination of a hardware device, e.g., an integrated circuit, and computer instructions and data that reside as read-only software on that device. Such software cannot be modified by the computer during processing.

FMEA Failure Mode and Effect Analysis
Used to identify failure modes and their consequences or effects. FMEA is a bottom-up technique: what can go wrong on a low level component and how this impacts the system or application

FTA Fault Tree Analysis
Top-down technique. The analyst looks at the high-level system failure and proceeds down into the system to trace failure paths.

Functional specifications A written definition of the function that a system or system specification component can perform

Functional testing Also known as black box testing because source code is not needed. Involves inputting normal and abnormal test cases, then evaluating outputs against those expected. Can apply to computer software or total system.

GALP Good Automated Laboratory Practice

GAMP Good Automated Manufacturing Practice

GAP Good Analytical Practice

GCP Good Clinical Practice

GMP Good Manufacturing Practice

Good Clinical Practices (GCPs) Term used to describe a collection of loosely related regulations that define the responsibilities of those involved in a clinical trial. The regulations include those that govern institutional review boards, informed consent, and sponsors and monitors. Refer to 21 CFR Parts 50 and 56.

Good Laboratory Practices (GLPs) Regulations of the U.S. Food and Drug Administration and other countries that spell out the requirements for nonclinical (animal or laboratory) studies that will be submitted to the regulatory agency to support a marketing application. The U.S. GLPs are found in 21 CFR Part 58.

Good Manufacturing Practices (GMPs)
1. Also known as current good manufacturing practices (cGMPs). U.S. regulations in 21 CFR Part 211 contain the minimum current good manufacturing practices for methods, facilities, and controls to be used for the manufacture, processing, packing, or holding of a drug to assure that it meets the requirements of the Federal Food, Drug, and Cosmetic Act for safely and has the identity and strength and meets the quality and purity characteristics that it claims. There are good manufacturing practices for medical devices found in 21 CFR Part 820 and for blood and blood products found in 21 CFR 606.
2. European Community Guide to Good Manufacturing Practice for Medicinal Products is the fourth volume of the Rules Governing Medicinal Products in the European Community. It is an EC Guide approved by representatives of the pharmaceutical inspection services of the member states of the EU.
3. The phrase is used generally for rules, regulations, or guidelines on the subject issued by any government.

HACCP	Hazard analysis and critical control points
Hazard	The potential source of harm (ICH)
HPLC	High performance liquid chromatography
ICH	International Conference for Harmonisation. 1. Provides a forum for a constructive dialog between regulatory authorities and the pharmaceutical industry on the real and perceived differences in the technical requirements for product registration in the EU, United States, and Japan. 2. Identifies areas where modifications in technical requirements or greater mutual acceptance of research and development procedures could lead to a more economical use of human, animal, and material resources, without compromising safety. 3. Makes recommendations on practical ways to achieve greater harmonization in the interpretation and applications of technical and requirements for registration.
ILAC	International Laboratory Accreditation Cooperation. Working for international acceptance of data generated by accredited organizations.
Interlaboratory test comparisons	Organization, performance, and evaluation of tests on the same or similar items or materials by two or more laboratories in accordance with predetermined conditions.
Internal audit	A periodic process carried out by laboratory staff to check that the laboratory's quality assurance system is effective, documented, and adhered to by all staff.
International standard	Standard that is adopted by an international standardizing/standards organization and made available to the public.
Inspection	Structured peer reviews of user requirement specifications, design specifications, and documentation
Installation qualification (IQ)	Installation qualification establishes that the instrument is delivered 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.
ISO	International Organization for Standardization. Agency responsible for developing international standards; founded in 1947.
ISO 9000 Series standards	The ISO 9000 series quality standards apply internationally. They are relevant not just for laboratories but for all types of manufacturing and service organizations.

ISO/IEC Standard 17025 *General Requirements for the Competence of Calibration and Testing Laboratories.* Like the ISO 9000 series standards, compliance with ISO/IEC 17025 is voluntary. It is specifically intended only for calibration and testing laboratories. ISO/IEC 17025 is typically used as a guide against which a laboratory's quality system can be evaluated.

ISPE International Society for Pharmaceutical Engineering

IUPAC The International Union of Pure and Applied Chemistry

JP Japanese Pharmacopeia

(Laboratory) accreditation Formal recognition that a testing laboratory is competent to carry out specific tests or types of tests.

LGC UK Laboratory of the Government Chemist

LIMS Laboratory Information Management System

LOD Limit of detection. The lowest concentration of an analyte that the analytical procedure can reliably differentiate from the background noise.

LOQ Limit of quantification. The amount of an analyte in a sample that can be determined with previously specified precision.

MOH Ministry of Health, the most commonplace designation for a country's Health Regulation Authority.

NBS The United States National Bureau of Standards which is, today, called National Institute of Standards and Technology (NIST).

NIST National Institute for Standards and Technology in the United States. Formerly called the National Bureau of Standards (NBS). Responsible for establishing a measurement foundation to facilitate both national and international commerce.

NVLAP National Voluntary Laboratory Accreditation Program. A federal program under which NVLAP operates as an unbiased third party to accredit both calibration and testing laboratories (http://ts.nist.gov/nvlap).

Obsolescence The final phase in a system's life cycle when the system is retired from use and taken off the market. At Hewlett-Packard, an obsolescence plan documents the support activities guaranteed for up to 10 years following obsolescence.

OECD Organization for Economic Co-operation and Development

OOS Out of specification

OOT Out of trend

Operational qualification (OQ)	Process of demonstrating that an instrument will function according to its operational specifications in the selected environment.
Out-of-control	Reference to a situation in which compliance with GMPs is not evident. The facility or operation is considered to be out of control.
PASG	(UK) Pharmaceutical Analytical Sciences Group
Performance Qualification	Process of demonstrating that an instrument consistently performs according to a specification appropriate for its routine use.
PHA	Preliminary Hazard Analysis Can be used to identify hazards and to guide development of countermeasures to mitigate the risk posed by these hazards.
Pharmacopeia	Official compilation of medicinal substances and/or articles with descriptions, tests, and formulas for preparing them, selected by a recognized authority. The pharmacopeia issued for a country is the legal standard of that nation. Also spelled *pharmacopoeia*.
PIC	Pharmaceutical Inspection Convention, a multinational organization whose members have agreed to mutual recognition of facility inspections for good manufacturing practice.
PIC/S	Pharmaceutical Inspection Cooperation Scheme. Mission: To lead the international development, implementation and maintenance of harmonised Good Manufacturing Practice (GMP) standards and quality systems of inspectorates in the field of medicinal products.
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. Now known as the Pharmaceutical Research and Manufacturers Association of America (PhRMA)
PQ	Performance Qualification
Precision	The degree of agreement of a measured value with other values recorded at the same time, or in the same place or on similar instruments. Also referred to as repeatability.
Proficiency testing	A systematic testing program in which samples are analyzed by a number of laboratories to measure the competence to undertake certain analyses.
Prospective validation	Establishing documented evidence that a system does what it purports to do based on a validation plan.

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.

Quality assurance (QA) A set of activities, often performed by employees in a similarly named department, that check that the characteristics or qualities of a product actually exist at the time the product is sold. Oversight function that audits operations to determine that procedures and systems are suitable and recommends required changes to provide evidence that the quality function is functioning correctly. QA is involved from product concept through design, manufacture, and distribution until the ultimate use of the product by the patient.

Quality control (QC) Day to day control of quality within a company, responsible for the acceptance or rejection of incoming raw materials and packaging components, in-process tests, labeling, and inspection, assurance that systems are being controlled and monitored, and for the approval or rejection of finished dosage forms. A laboratory-based function.

Raw data Any laboratory worksheets, records, memoranda, notes, or exact copies thereof that are the result of original observations and activities of a non-clinical laboratory study and are necessary for the reconstruction and evaluation of the report of that study. It may include photographs, microfilm, or microfiche copies, computer printouts, magnetic media, including dictated observations, and recorded data from automated instruments.

RCRA Resource Conservation and Recovery Act

Recovery The extraction efficiency of an analytical process, reported as a percentage of the known amount of an analyte carried out through the sample extraction and processing steps of the procedure.

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.

Reference standard A standard, generally of the highest metrological quality available at a given location, from which measurements made at that location are derived.

Regulatory methods validation	Process whereby submitted analytical procedures are first reviewed for adequacy and completeness and then are tested as deemed necessary in U.S. Food and Drug Administration laboratories. Depending in part on the quality of submitted data, validation may range from step-by-step repetition of an assay procedure to more elaborate studies that include assessment of accuracy, precision, sensitivity, and ruggedness of the method.
REMCO	Council Committee of Reference Materials of the International Organisation for Standardization, established in 1976. The committee has since published several guides on the nomenclature, certification, and uses of reference materials.
Reproducibility	Precision between laboratories
Retrospective validation	Establishing documented evidence that a system does what it purports to do based on review and analysis of historic information.
Revalidation	A repetition of validation necessary after the process has been changed, for example, when a manual system is upgraded to an automated system.
Risk assessment	Systematic process or organizing information to support a risk decision within a risk management process (ICH).
Risk analysis	The estimation of risk associated with the identified hazards (ICH)
Risk control	Actions of implementing risk management decision (ICH)
Risk evaluation	Compares the estimated risk against given risk criteria using a qualitative or quantitative scale to determine the significance of risk (ICH)
Risk identification	Systematic use of information to identify potential sources of harm (hazards) referring to the risk question or problem description (ICH)
RSD	Relative Standard Deviation
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. Required under GLP guidelines.
SIG	Special Interest Group, SIGs have been established by GAMP to develop Good Practices Guides for the industry on various topics.
Source code	An original computer program in a legible form (programming language), translated into machine-readable form for execution by the computer.
SRM	Standard Reference Material
SSC	System Suitability Checking

Standard Operating Procedure (SOP) Documented instructions that should be followed when operating a process for the process to be considered valid. Required under GLP regulations. Written documents that prescribe the detailed methods and action steps to be followed in order to accomplish a particular task. The U.S. Food and Drug Administration requires SOPs for virtually every aspect of production, control, and testing of pharmaceutical products. One of the SOPs should describe the issuance and control of SOPS.

Stock solution The original solution prepared directly by weighing the reference standard of the analyte and dissolving it in appropriate solvents.

System suitability testing A process of checking out the performance specifications of a system, often called method validation when applied to a particular separation and called system validation when applied to a separation system used routinely.

TGA (Australian) Therapeutic Goods Administration

Test A technical operation that consists of the determination of one or more characteristics or performance of a given product, material, equipment, organism, physical phenomenon, process, or service according to a specified procedure.

Test plan A document prescribing the approach to be taken for intended testing activities. The plan typically identifies the items to be tested, the testing to be performed, test schedules, personnel requirements, reporting requirements, evaluation criteria, and any risks requiring contingency planning.

Traceability The property of a result of a measurement whereby it can be related to appropriate standards, generally international or national, through an unbroken chain of comparisons all having stated uncertainties.

UKAS United Kingdom Accreditation Service. The national accreditation body for the U.K. Formed in 1995 by the amalgamation of the National Measurement Accreditation service (NAMAS) and the National Accreditation Council for Certification Bodies (NACCB).

Uncertainty Measurement uncertainty is an estimate to a measurement which characterizes the range of values within which the true value is asserted to lie (ISO/DIS 254-1).

URS User Requirement Specifications

USP	United States Pharmacopeia. Official compendium recognized by the Federal Food, Drug, and Cosmetic Act. Serves as the basis for enforcement actions by the U.S. Food and Drug Administration involving official (USP) drugs. Published every five years by the United States Pharmacopeial Convention, a non-profit organization. It is combined with the National Formulary. The USP is the official pharmacopeia of the United States and several other countries.
Validation protocol	Written plan stating how validation will be conducted, including test parameters, product characteristics, production equipment, and decision points on what constitutes acceptable test results.
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.
WELAC	Western European Laboratory Accreditation Corporation
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.
Working solution	Solution prepared from the stock solution through dissolution in the appropriate solvent.

Appendix B

OQ Tests for Selected Equipment

This appendix summarizes test procedures and acceptance limits for the operational qualification of selected equipment in a table format. At the beginning of this appendix you can find a few general recommendations that apply to all procedures.

Traceability of Standards

Typically standards used for operational qualifications performance tests should be certified or traceable to national standards. Test samples not used for quantitative do not need to be certified or traceable to national standards. An example is a sample that is used to determine the precision of peak area or peak retention time. Samples that are used for quantitative calibration of the system should be certified and/or traceable to national standards. An example is a standard that is used to determine the linearity of a detector. In those cases where external certification or traceability for such samples is not available, the laboratory should do the utmost to ensure accuracy of the standard. The procedure to ensure accuracy should be documented.

Acceptance Limits

Acceptance limits are determined by the intended use and may be more stringent than the ones that are recommended in the tables

Documentation and Archiving

In a summary report, the acceptance limits and the actual results should be documented. The report should also include the date of measurement and the name of the operator. The report should also have a reference to the instrument identification and measurement method.

If the actual results have been calculated from a series of measurements, the results of the individual measurements should be archived for later

recalculation, if necessary. For example, when the standard deviation of an injection precision of a gas chromatography autosampler is calculated from six replicate injections, the peak area of individual measurements should be recorded and archived.

Gas Chromatography (GC)

Precision of peak retention times	
Test procedure	1. Five injections of a standard 2. Calculation of relative standard deviation
Acceptance limits	<1% RSD
Test frequency	yearly
Remarks	

Precision of peak areas	
Test procedure	1. Five injection of a standard 2. Calculation of relative standard deviation
Acceptance limits	<2% RSD
Test frequency	yearly
Remarks	

Accuracy of the temperature of the column oven	
Test procedure	Measure temperature in column oven and compare with setpoint.
Acceptance limits	±1°C
Test frequency	yearly
Remarks	The temperature measurement device should be calibrated and traceable to a national standard.

Gas Chromatography – Headspace Analysis

Accuracy of heated zone temperature	
Test procedure	Measure and compare actual temperature with setpoints at 50, 70, and 90 ºC.
Acceptance limits	3ºC
Test frequency	yearly
Remarks	The temperature measurement device should be calibrated and traceable to a national standard

(*Continued*)

Gas Chromatography – Headspace Analysis (*Continued*)

Precision of heated zone temperature	
Test procedure	Measure and compare actual temperature with setpoints at 50, 70, and 90ºC.
Acceptance limits	2ºC
Test frequency	yearly
Remarks	The temperature measurement device should be calibrated and traceable to a national standard.

Precision of injection	
Test procedure	• Five injections of a standard • Calculation of relative standard deviation
Acceptance limits	<2% RSD
Test frequency	yearly
Remarks	

Carryover of injection	
Test procedure	Inject blank solvent after standard. Measure peak ratio between blank and standard injection.
Acceptance limits	<5%
Test frequency	yearly
Remarks	

Capillary Electrophoresis

Stability of voltage	
Test procedure	Plot of voltage
Acceptance limits	< 0.25 kV
Test frequency	six months
Remarks	

Precision of peak areas	
Test procedure	1. Five injection of a standard 2. Calculation of relative standard deviation
Acceptance limits	< 2% RSD
Test frequency	yearly
Remarks	

UV/Visible Spectrophotometer

Wavelength accuracy - holmium oxide solution

Test procedure	Measure wavelength maxima of holmium oxide solution at 241, 287, 361, and 536 nm.
Acceptance limits	±1 nm in UV range ±3 nm in visible range
Test frequency	six months
Remarks	Standard should be traceable to national standard.

Wavelength accuracy - holmium oxide filter

Test procedure	Measure wavelength maxima of holmium oxide filter at 361, 418, and 536 nm.
Acceptance limits	±1 nm in UV range ±3 nm in visible range
Test frequency	six months
Remarks	Filter should be traceable to national standard.

Absorption intensity

Test procedure: Measure absorption of potassium chromate solution.

Acceptance limits:

wavelength	*A 1%/1cm*	*Limits*
235 (min)	124.5	122.9–126.2
257 (max)	144.0	142.4–145.7
313 (min)	48.6	47.0–50.3
350 (max)	106.6	104.9–108.2

Test frequency: six months

Remarks: Standard should be traceable to national standard.

Stray light

Test procedure	Measure absorption of 1.2% Potassium Chloride solution at 200 nm against water
Acceptance limits	Absorption at 200 nm > 2.0 AU
Test frequency	six months
Remarks	Alternative standards • Sodium nitrite • Sodium iodide

(*Continued*)

UV/Visible Spectrophotometer (*Continued*)

Control of cuvette	
Test procedure	Transmission of cuvette (water) against air
Acceptance limits	a) quartz cuvettes 85% at 220 nm 88% at 240 nm b) glass cuvettes 85% at 356 nm 88% at 650 nm
Test frequency	six months
Remarks	

Wavelength resolution	
Test procedure	Measurement of toluene spectrum from 260 to 275 nm. Calculation of ratio peak height to valley.
Acceptance limits	Absorbance ratio peak to valley at 266/269 nm >1.5
Test frequency	six months
Remarks	

High Performance Liquid Chromatography (HPLC)

Accuracy of the flow rate	
Test procedure	Measurement of flow rate with a volumetric flask and stop watch or with calibrated digital flow meter.
Acceptance limits	±5C
Test frequency	yearly
Remarks	This test typically is performed at the beginning of the system test procedures. Successful completion proves that there is no major leak in the system.

Precision of flow rate	
Test procedure	1. Five injections of a standard 2. Calculation of relative standard deviation
Acceptance limits	<2% RSD
Test frequency	yearly
Remarks	Recommended standard: caffeine

(*Continued*)

High Performance Liquid Chromatography (HPLC) (*Continued*)

Precision of peak areas	
Test procedure	1. Five injections of a standard 2. Calculation of relative standard deviation
Acceptance limits	<2% RSD
Test frequency	yearly
Remarks	Recommended standard: caffeine

Accuracy of the temperature of the column oven	
Test procedure	Measure temperature in column oven and compare with setpoint.
Acceptance limits	±1°C
Test frequency	yearly
Remarks	1. column temperature accuracy is 2. The temperature measurement device should be calibrated and traceable to a national standard.

Precision of the temperature of the column oven	
Test procedure	Measure temperature in column over 20 min at 40°C.
Acceptance limits	±0.5°C
Test frequency	yearly
Remarks	

Baseline noise	
Test procedure	Plot baseline for 20 min. Measure peak to peak noise in sections of 1 min. Average results.
Acceptance limits	$\pm 1 \times 10 - 4$°C
Test frequency	yearly
Remarks	(ASTM E19.09)

Detector linearity	
Test procedure	Inject 5 standards of caffeine. Plot response factor versus amount.
Acceptance limits	≤1.5 AU with 5% level.
Test frequency	yearly
Remarks	Standards should be certified.

(*Continued*)

High Performance Liquid chromatography (HPLC) (*Continued*)

UV/Visible detector wavelength accuracy	
Test procedure	Scan compound with known spectrum. Measure wavelength at absorption maximum. Compare actual value with reference value.
Acceptance limits	±2 nm
Test frequency	three months and whenever the detector is moved
Remarks	1. Known standard should be certified. 2. Caffeine is a good standard for 250 to 300 nm. 3. Built in holmium oxide filters can be used for automated checks.

Autosampler carryover	
Test procedure	Inject blank solvent after standard. Measure peak ration between blank and standard injection.
Acceptance limits	<0.3%
Test frequency	yearly
Remarks	Caffeine has been proven to be a good standard.

Mobile phase composition accuracy	
Test procedure	Run step gradients at 10, 11, 50, and at 90% with acetone tracer, step heights relative to 100%.
Acceptance limits	±2%
Test frequency	yearly
Remarks	The analytical column should be replaced by empty tubing. Back-pressure should be >20 bar.

Liquid Chromatography/Mass Spectrometry

Stability of voltage	
Test procedure	Measure mass of reference standard (calibrant) and compare with well-characterized reference file. Reference Standard depends on mass type of detector. Examples: PerFluoroTriButylAmine (PFTBA), Polyethylenglycol (PEG)s, or actual analyte.
Acceptance limits	Depends on type of detector. Example: resolution determined m/z of calibrant ion shall be within 0.1 amu of theoretical.

(*Continued*)

Liquid Chromatography/Mass Spectrometry (*Continued*)

Stability of voltage	
Test frequency	Daily if the MS is used to perform full scan mass spectra Less frequently if connected to an LC and used in SIM mode
Remarks	Calibrants should be well-characterized reference materials. PPG and PEG are most widely used for ESI-MS calibration.

Infrared/Near infrared

Wavelength accuracy	
Test procedure	Measurement of Polystyrene spectrum at 1144, 1680, 2167, and 2307 nm. Comparison of results with reference values.
Acceptance limits	± 2 nm
Test frequency	daily
Remarks	Standard should be traceable to national standard.

Control of 0 and 100%	
Test procedure	Control at 0 and 100%
Acceptance limits	1% transmission (measured at 4000 cm^{-1})
Test frequency	daily and after changing measurement parameters
Remarks	

Wavelength resolution	
Test procedure	Resolution of Polystyrene at 2870/2851 and at 1589/1883 nm
Acceptance limits	• T (band 2870 cm^{-1} − band 2851 cm^{-1}) 18 • T (band 1589 cm^{-1} − band 1583 cm^{-1}) 12
Test frequency	daily
Remarks	

Analytical Balance

Accuracy	
Test procedure	Measurement of reference weight, use 10 mg, 50 mg, 100 mg, 500 mg, 1 g, 5 g, 10 g, and 20 g. Compare the actual results with reference weights.
Acceptance limits	0.1 %

(*Continued*)

Analytical Balance (*Continued*)

Test frequency	daily or when used, whatever is longer with internal reference weights yearly with traceable external weights through instrument vendor
Remarks	External standard should be traceable to national standard.

Flame Atomic Absorption Spectrophotometer

Calibration	
Test procedure	As stated in analytical method
Acceptance limits	see vendor specifications
Test frequency	six months
Remarks	Standard as stated in analytical method

Linearity	
Test procedure	As stated in analytical method
Acceptance limits	see vendor specifications
Test frequency	daily
Remarks	Standard as stated in analytical method as defined in method validation

Laboratory Ovens

Temperature accuracy	
Test procedure	Measure the temperature inside the oven over the full temperature working range using at least six different temperatures and compare with setpoints. Plot a curve of actual oven temperature versus setpoints.
Acceptance limits	$\pm 2^{\circ}$C. If deviations are higher, the measured data points should be plotted as calibration curve. The curve should be used for actual temperature adjustments.
Test frequency	six months
Remarks	1. Thermometer should be calibrated and traceable to national standard. 2. For critical applications, one calibrated thermometer should be mounted inside the oven for continuous monitoring.

Laboratory Furnaces

Temperature accuracy	
Test procedure	Measure the temperature inside the furnace over the full temperature working range using at least six different temperatures and compare with setpoints. Plot a curve of actual oven temperature versus setpoints.
Acceptance limits	±5°C. If deviations are higher, the measured data points should be plotted as calibration curve. The curve should be used for actual temperature adjustments.
Test frequency	yearly
Remarks	1. Thermometer should be calibrated and traceable to national standard. 2. For critical applications one calibrated thermometer should be mounted inside the oven for continuous monitoring.

Sterilizers (hot air)

Temperature accuracy	
Test procedure	Measure the temperature inside the sterilizer using a thermometer. Measure the temperature inside the sterilizer at various locations using a thermocouple.
Acceptance limits	±2°C
Test frequency	• daily with thermometer • bimonthly with thermocouple
Remarks	Thermometer should be calibrated and traceable to national standard.

Refrigerators and Freezers

Temperature accuracy	
Test procedure	Measure the temperature inside the refrigerator over the full temperature working range using at least six different temperatures and compare with setpoints. Selected temperature range may be 4 to 20°C. Plot a curve of actual oven temperature versus setpoints.
Acceptance limits	±2°C
Test frequency	yearly
Remarks	1. Thermometer should be calibrated and traceable to national standard. 2. For critical applications, one calibrated thermometer should be mounted inside the refrigerator or freezer for continuous monitoring. Some accreditation schemes require daily or weekly monitoring of the temperature.

Thermometers and Thermocouples

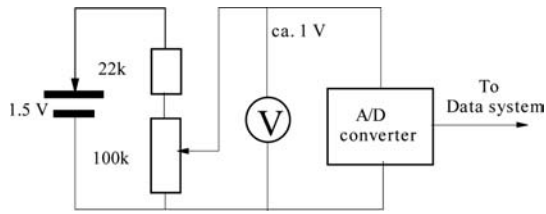
Temperature accuracy	
Test procedure	Measure the temperature of the thermometer over the full working range at characteristic reference points, e.g., at the ice point (0°C).
Acceptance limits	±1°C at 30 to 40°C, ±2°C at 100°C
Test frequency	yearly
Remarks	1. In addition to the specified in-house procedure the thermometer should be calibrated by external organizations (e.g., by an accredited laboratory) at least every years. 2. Some applications require better accuracy than those specified under acceptance limits, for example, the temperature of incubation at some microbiological tests should be as tight as ±0.25°C. In this case, the thermometers should be calibrated by an external service. 3. Temperature reference points

triple point of equil. hydrogen	−259.34°C
boiling point of oxygen	−182.96°C
melting point of water	0°C
boiling point of water	100.0°C
freezing point of zinc	419.58°C
freezing point of silver	961.93°C
freezing point of zinc	1064.43°C

Karl Fisher Apparatus

Calibration and precision	
Test procedure	Add known amount of water (ca 50 mg, 1 drop) to 100 ml anhydrous methanol. Titrate the water with Karl Fisher reagent (e.g., pyridine based). Calculate the water equivalence factor f using the formula water (mg)/ml KF reagent. The measurement should be performed three times and the results should be averaged.
Acceptance limits	Precision < 1 % RSD
Test frequency	before each use
Remarks	

Analog/digital Converter

Analog input - A/D converter	
Test procedure	1. Generate a voltage of about 1 V with commercial battery and voltage separator. 2. Apply the voltage to the analog input and read the value at the data system. 3. Compare the value at the data system with the voltmeter. 4. Zero V measurement at the analog input.
Electrical diagram	
Acceptance limits	±3%
Test frequency	yearly
Remarks	1. Use calibrated voltmeter. 2. The environmental temperature should be stable (±1°C over the time of measurement cycle). 3. There should not be any electromagnetic interference. 4. Don't touch electrical cables and voltage separator during the measurement cycle. 5. Use new battery for each measurement. 6. Remove the battery after the measurement.

Source: Ref. 97.

Dissolution Testing

Temperature accuracy	
Test procedure	Measurement of temperature in test sample and water bath with calibrated thermometer at 37°C.
Acceptance limits	37°C ± 0.5°C
Test frequency	six months
Remarks	According to USP and German DAB Thermometer should be traceable to national standard

(*Continued*)

Dissolution Testing (*Continued*)

Accuracy of shaft rotation

Test procedure	Measurement of shaft rotation at 50 and 100 turns per minute with rotation measurement device and stopwatch comparison of results with setpoint.
Acceptance limits	±4%
Test frequency	six months
Remarks	

Control of distance of shaft from side of vessels

Test procedure	Measurement of the distance of the stirrer.
Acceptance limits	25 mm ±2 nm
Test frequency	before each measurement (according to German DAB)
Remarks	German DAB requirement (before each measurement) is very time consuming.

Control of paddle centering

Test procedure	Difference between the axis of the rod and the axis of the vessel.
Acceptance limits	< 2 nm
Test frequency	before each measurement
Remarks	

Control of instrument suitability

Test procedure	Measurement of the dissolution rate with salicylic acid tablets and Pednison tablets. 30 minutes at 37°C.
Acceptance limits	Compound specific, according to USP and actual SOP
Test frequency	before each measurement
Remarks	

Viscosimeter

Accuracy

Test procedure	Measurement with calibrated oils 4–5 measurements
Acceptance limits	Std of individual measurements: ±1% Deviation from accurate value: ±2%
Test frequency	Yearly
Remarks	1. According to Ph. Eur. 5, and 2. Oils should be traceable to national standard (available from vendors).

Melting Point

Accuracy	
Test procedure	Measurement of melting point of reference compounds of the world health organization • Heating rate: 1°C/min • Temperature: 5°C below the melting point • Vanilline: 1.5° range from 81.0 to 83.0°C • Acetanilide: 1.0° from 114.0 to 115.5°C • Phenacetin: 1.5° from 134.0 to 136.0°C • Sulfanilamide: 1.5° from 164.6 to 165.5°C • Sulfapyridine: 1.5° from 190.2 to 192.5°C • Caffeine: 1.0° from 123.5° C to 237.0°C (Ref.: Mettler FP81)
Acceptance limits	0.5°C
Test frequency	three months
Remarks	Benzoic acid also suitable

pH Meter

Accuracy	
Test procedure	Calibration with buffer solution at pH 7 and pH 4. Verification with buffer solution at pH 5 or pH 6.
Acceptance limits	<0.05 pH units
Test frequency	before each use
Remarks	1. Buffer solutions are commercially available in either tablet or solution form. 2. Some pH meters also have a temperature sensor. This should be calibrated every six months. 3. The electrodes should be washed between each measurement and the buffers should be visually checked for cleanness and absence of microbial growth before each use.

Refractometer

Accuracy according to USP

Test procedure	Measurement of de-ionized water at 20°C ±0.1°C at U = 589.3 nm (Frauenhofer line of sodium light) Expected refractive index: $n_D(20) = 1.3330$
Acceptance limits	$n_D(20) = 1.3329$ to 1.3331 ±5 units of the fourth digit
Test frequency	monthly
Remarks	USP 28 <831>

Refraction Index

Test Procedure	Ph. Eur. 5, Edition 2.2.6. 20°C ± 0.5°C, U 589.3 nm	
Acceptance limits	*Compound*	*Dn/DT* Temperature coefficient
	Trimethylpentane	−0.00049
	Toluene	−0.00056
	Methylnaphthalene	−0.00048
Test frequency	yearly	
Remarks	German DAP 1966 V 6.5	
Remarks	German DAP 1966 V 6.5	

Polarimeter

Accuracy

Test procedure	Measurement of calibrated control quartz Reference value $[\#]_D(20) = 14.986°$
Acceptance limits	$[\#]_D(20) = 14.97$ to 15.00°
Test frequency	3 months
Remarks	Quartz should be traceable to national standard.

Linearity

Test procedure	Measurement of Sacharose-Solution according to Ph.Eur.1, Vol. I (1974), layer-thickness 1.00 dm		
Acceptance limits	*C g/100ml*	*$[\#]_D(20)$*	*Tolerance*
	20.0	13.32°	±0.027°
	30.0	19.95°	±0.040°
	40.0	26.56°	±0.050°
Test frequency	6 months		
Remarks			

Declaration of Operational Qualification

At the end of the OQ tests, a Certificate of Declaration of Operational Qualification should be developed to document the tests. An example is shown below.

Declaration of Operational Qualification

Equipment	Balance
Serial number	XZ ddd
Asset number	5634–44
Date	11.19.2005
Method/SOP Number	LAB567
Results and evaluation	The result meets the requirements.
Attachments	Protocol and table with reference and actual values Print-outs
Date of next qualification	11.18.2006

Signatures

Technician	Name: L. Jones	Signature: *Lou Jones*
Manager	Name: B. Miller	Signature: *Brenda Miller*

Appendix C

Selected (Standard) Operating Procedures

Operating procedures, or SOPs, play a major role in an analytical laboratory's quality system. They are required by all good practice regulations and quality and accreditation standards. They are developed to ensure that laboratory operations are conducted with consistently good planning, appropriate distribution, and execution and complete documentation. Most laboratory audits and inspections will check if appropriate SOPs exist and are followed.

This appendix gives some recommendations on SOPs, including a list of operating procedures for analytical equipment. Examples of SOPs are provided for the validation of methods and simple and complex application software, for retrospective evaluation and validation of existing computer systems, and for testing of hardware. (SOPs are available in electronic format from the author.)

GENERAL RECOMMENDATIONS

Organization/Format

- At first, an SOP should be developed on how to develop, test, write, publish, distribute, maintain, and archive SOPs. This ensures that all SOPs are handled in the same way.
- Develop and communicate a numbering and naming system for SOPs.
- Do not prepare too many SOPs. Think twice before you prepare an SOP for a special job (too much paperwork does not improve the efficiency of a laboratory or the quality of analytical data).
- Where possible, combine individual procedures into a single, larger SOP.
- The format should be consistent for all SOPs. All SOPs should include some general elements such as a meaningful title, scope, purpose (objective), procedural text, and references (if any).

- The text should describe the sequence of tasks in a step-by-step format.
- All pages should be numbered, by page and the total number of pages (e.g., page 1 of 3).

Content/Level of Detail

- For equipment calibration, testing, and maintenance, develop one and only one SOP for each type of equipment. It should be independent from the instrument's use and manufacturer.
- Do not use the vendor's specifications as acceptance limits for equipment testing. This may require frequent preventive maintenance to meet the stringent specifications. Acceptance limits should be based on the intended use of the equipment.
- Do not be too detailed; this avoids the need for frequent updates. For example, an SOP for purchasing chemicals should not include any vendor's name, thus avoiding an update if the vendor changes.
- Do not be too restrictive. This requires users to spend too much time writing and authoring deviations. This is especially important for acceptance limits of equipment.
- SOPs not only describe what to do but how to do it.
- Instrument SOPs should be written close to the instrument in the laboratory, not in the office. They should be either written or thoroughly reviewed by somebody who has a good understanding of the technical work. SOPs should not explain how procedures are supposed to work, but how they work in reality.
- SOPs should be written so they are understood by typical users.
- SOPs should be written in a language that is understandable by the user.
- SOPs for equipment testing should include forms and templates for entries of dates, results, comments, further actions (in case the specifications are not met), and signatures.
- Books, instrument operating manuals, and other literature can be used as references. However, it should be ensured that the references will be accessible during the entire archiving period.

Development and Testing

- Draft SOPs should be circulated to the target audience prior to the test release to collect inputs.
- SOPs should be tested by typical users prior to their final release.

Approval

- SOPs should be signed by the author and approved and signed by the management. Some companies also require the QA department to review and sign SOPs before they are submitted to the management.

- Copies of equipment SOPs should be located close to the instruments for easy access by operators.
- Deviations from SOPs should be explained and authorized.

Distribution, Use and Archiving

- The distribution of SOPs should be handled by the QA department. This ensures that the distribution list is always the same and that all users always have the same version.
- Old SOPs should be returned to the QA department or scratched.
- QA should verify through audits that the most-up-to-date SOPs are used.
- QA should verify through audits that SOPs are followed.
- If SOPs are distributed electronically, the users should be notified by electronic mail that a new or revised SOP is available on a specified server.
- It is a good practice to have one copy of each actual SOP stored in paper format at a central place that is easily accessible by all users.
- There should be a list of all SOPs with titles and numbers easily accessible by users.
- SOPs must be archived.

Maintenance and Periodic Review

- SOPs should be reviewed periodically to determine if the written procedure still reflects laboratory practices.
- The person responsible for the SOP should keep a record of all reviews and changes.

TYPES AND/OR CONTENT OF SOPs

SOPs can be developed for the following:

Administration

- Responsibilities
- Development and handling (distribution, archiving, etc.) of SOPs
- Naming and numbering system for SOPs

Equipment

- Purchasing of equipment and chemicals
- Qualification of a vendor
- Writing requirement specifications
- Software development and validation (life cycle)

- Installation and operational qualification of equipment
- Retrospective evaluation and validation of existing systems
- Routine inspection, testing, maintenance, and calibration
- Actions to be taken in response to equipment failure
- Change control
- Log-books and instrument repair

Data

- Definition of raw data
- Entry of data and proper identification of individuals
- Entering the data
- Data review
- Changing data

Analytical Methods

- Development and validation of analytical methods
- Verification of standard methods
- Validation of ad hoc methods
- Transfer of methods

Handling of Samples and Standards

- Receipt and distribution of test and control samples
- Labeling of reagents and samples
- Sample collection and tracking
- Preparing standard solutions
- Processing and analyzing specific matrices and samples

Safety

- General laboratory safety issues
- Chemical hazard handling (e.g., purchasing, classification, inventory, disposal)
- Safety of visitors (safety sheets, clothing, glasses)

Security

- Limited access to buildings, equipment, and data
- Generation and distribution of passwords
- Check of computer systems for viruses
- Program, method, and data backup
- Disaster recovery

Personnel

- Development and communication of job descriptions
- Training of personnel

QA Audits and Reviews

- Audit master schedule
- Data review and reports
- Archiving audit reports

Archiving

- Archiving system
- Submission and retrieval
- Limited access
- Storage conditions and verification
- Retrieval of documents from the archive

PROPOSAL FOR A TITLE PAGE

<table>
<tr><td colspan="4">Title</td></tr>
<tr><td>Company</td><td>Company stamp (colored, to identify black copies)</td><td>Code (ID)</td><td>Valid from</td></tr>
<tr><td>Labor</td><td>Versions-Number</td><td colspan="2">Versions-Number replaced by this SOP</td></tr>
<tr><td>Developed by

Signature:
Signature:
Date:</td><td>Authorized by

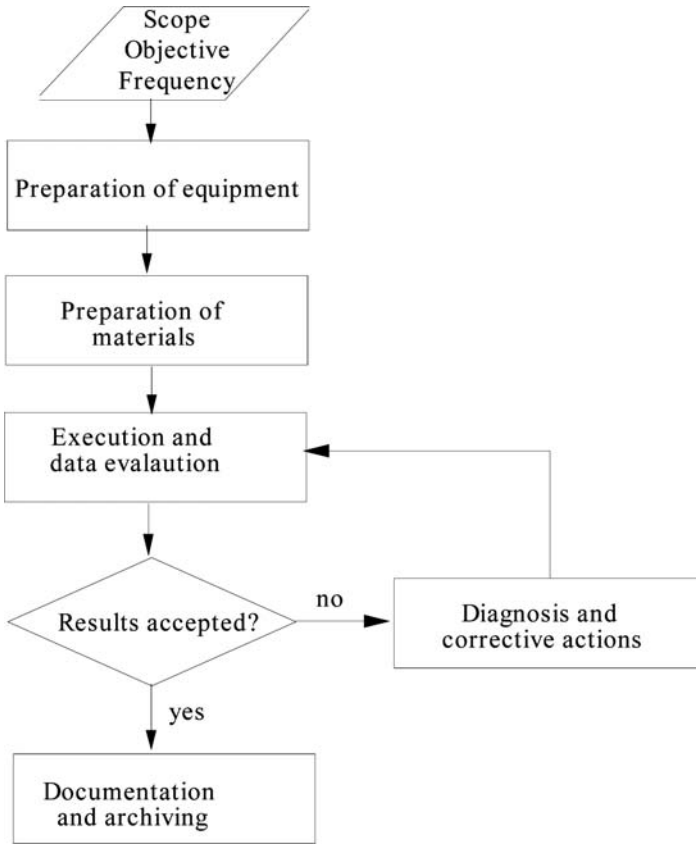
Signature:
Signature:
Date:</td><td colspan="2">Distribution list

----</td></tr>
<tr><td colspan="4">1. Scope

2. Purpose

Procedural text</td></tr>
<tr><td colspan="4">Page 1 o x</td></tr>
</table>

GENERAL WORKFLOW OF SOPs FOR EQUIPMENT TESTING



Example #1: SOP for the Preparation of Standard Operating Procedures

The development, testing, publishing, and distribution of SOPs should follow documented procedures. The format, structure, and some content elements should be consistent. An example is shown on the following pages. This is a proposal and starting point only and may need adaptation to different SOPs. There is no assurance expressed that the operating procedure will pass a regulatory inspection.

1. Scope

Analytical laboratories: all departments, routine procedures

2. Purpose

Regulations and quality and accreditation standards applicable to analytical laboratories require various routine laboratory activities to follow (standard) operating procedures. The development, publishing, distribution, maintenance, and archiving of such SOPs should follow documented procedures. The format, the structure, and some content elements should be consistent within a laboratory. This SOP addresses the process for generation and maintenance of SOPs.

3. Frequency

a) When generating a new SOP
b) When revising an existing SOP

4. Format

The SOP consists of a title page and procedural text.

a) The title page includes
    1. The company name
    2. The title of the SOP
    3. Unique number and revision number
    4. Effective date
    5. The division and laboratory name
    6. The printed names and signatures of the author and a management representative
    7. The distribution list (by department)
    8. Page number and total number of pages
b) Each page includes:
    1. The company name
    2. The division name
    3. The laboratory name
    4. The title and ID code of the SOP
    5. The revision number
    6. The author
    7. The page number and total number of pages
c) The text part includes
    1. The scope
    2. The purpose
    3. Frequency of use
    4. Detailed procedure
    5. History of the SOP

5. Text of the SOP

a) Scope
   Defines applicability, for example, specific departments or test procedures.

b) Purpose
Defines the objective, for example, to test HPLC equipment.
c) Frequency
Defines the interval at which the SOP will be applied. Examples are 'daily,', 'monthly,', 'yearly,' or 'when used.'.
d) Detailed Procedure
    1. Material used, for example, chemicals
    2. Equipment used, for example, traceable test equipment
    3. Step by step instructions, for example, to calibrate a balance
    4. Evaluation procedure, if needed
    5. Acceptance procedure
    6. Documentation
e) History
Defines dates of first release and dates of all consecutive revisions.

6. Preparation

a) Confirm the need for the new or revised SOP.
b) Create a draft.
c) Submit the draft to the management representative.
d) The management distributes the draft to the staff for review and comments.
e) Comments are sent to the author.
f) The edited SOP is submitted to the management for review.
g) The edited SOP is submitted by the management to staff for review and testing, if appropriate.
h) The final version is approved and signed by the management.

7. Distribution

a) The management representative assigns a responsible person for the SOP.
b) The responsible person distributes paper copies to the QA department and to the laboratory manager.
c) The laboratory manager informs the responsible person on how many copies are required for the lab.
d) The responsible person creates the specified number of SOPs and distributes them.
e) If the newly distributed is a revision of an older one, the older one should be sent back to the SOP responsible person and discharged.
f) One copy is sent to the archive. The SOP archive retains all original SOPs, including revisions, in a historical file.
g) The SOP is entered into the company's electronic SOP database.

8. Maintenance, Review, and Update (change control)

a) Every 12 months, the author or a person designated by the management reviews the SOP and revises, if required.
b) SOPs may also be revised, if necessary (users of an SOP are encouraged to give feedback and to make enhancements requests as part of the laboratories quality policy).
c) Revisions follow sections 5, 6, and 7 of this SOP.

Example #2: Validation of Analytical Methods

Analytical methods should be validated prior to routine use. An example is shown on the following pages. This is a proposal and starting point only and may need adaptation to different SOPs. There is no assurance expressed that the operating procedure will pass a regulatory inspection.

1. Scope

a) Analytical chromatographic routine methods that are developed in-house
b) Standard chromatographic methods

2. Purpose

Accurate and consistent analytical data can only be obtained with validated methods. Regulations, quality, and accreditation standards applicable to analytical laboratories also require analytical methods to be validated prior to routine use and revalidated after a change. This SOP addresses the process for the validation of analytical methods.

3. Frequency

a) When new methods are developed in-house.
b) When standard methods are applied in-house
c) When methods are changed

4. Definitions

The following definitions are taken from the US Pharmacopeia (26) and from the ICH Conference (4):

a) **Method validation**
The US Pharmacopeia defined validation of analytical methods as "The process by which it is established, by laboratory studies, that the performance characteristics of the method meet the requirements for the intended applications."

b) **Specificity**
The ability to assess unequivocally the analyte in the presence of components which may be expected to be present. Typically these might include impurities, degradants, matrix, etc.

c) **Accuracy**
The accuracy of an analytical procedure expresses the closeness of agreement between the value which is accepted either as a conventional true value or an accepted reference value and the value found.

d) **Precision**
The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision, and reproducibility.

e) **Repeatability**
Repeatability expresses the precision under the same operating conditions over a short interval of time. Repeatability is also termed intra-assay precision.

f) **Intermediate precision**
Intermediate precision expresses within-laboratory variations: different days.

g) **Reproducibility**
Reproducibility expresses the precision between laboratories (collaborative studies usually applied to standardization of methodology).

h) **Limit of detection**
The limit of detection of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value.

i) **Limit of quantitation**
The limit of quantitation of an individual analytical procedure is the lowest amount of analyte in a sample which can be quantitatively determined with suitable precision and accuracy. The quantitation limit is a parameter of quantitative assays for low levels of compounds in sample matrices, and is used particularly for the determination of impurities and/or degradation products.

j) **Linearity**
The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample.

k) **Range**
The range of an analytical procedure is the interval between the upper and lower concentration (amounts) of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity.

l) **Robustness**
The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage.

5. Determination of the Scope, Objectives and Required Performance Characteristics

- Specify the objective of the method
- Specify the scope of the method
- Determine the performance characteristics and acceptance limits, for example, as shown in the below Table 1.

Table 1

Parameter	Acceptance limit
Specificity	
Accuracy	
∗amount 1	
∗amount 2	
∗amount 3	
Repeatability	
∗amount 1	
∗amount 2	
∗amount 3	
Intermediate precision	
∗amount 1	
∗amount 2	
∗amount 3	
Reproducibility	
Limit of detection	
Limit of quantitation (at a standard deviation of xx %)	
Linearity	
Range	

6. Preparation for the experiments

Materials:
Specify chemicals required for the experiments, their purity, and the source; allow for grade or source equivalency where applicable.
Specify the equipment as required for the experiments:

Example: Liquid Chromatograph HP1100 Series from Agilent Technologies, with peltier- cooled thermostatted autosampler, at least binary gradient, variable wavelength detector, thermostatted column compartment. Equipment must have past OQ test as described in SOP 453.

7. Determination of Method Performance Characteristics

Linearity and range:

a) Prepare five standard solutions A to E, containing the full working concentrations, for example, at the limit of quantitation (LOQ), the upper target concentration limit a, at a two concentrations between LOQ and x, and at 1.5 x a.
b) Inject each standard three times and measure the signal. Depending on the analysis technique this may be a signal height, a peak height, or just a digital value as read from a display.
c) Average the results.
d) Plot the area versus the concentration. Calculate the linear regression.
e) Calculate the response factors.

$$\text{Response Factor} = K = \text{Signal}/\text{amount}.$$

Compare the linear range with the specifications as set in 5.3.

Accuracy and recovery:

Obtain the 'true' value of a sample by one of these procedures:

a) Purchase certified reference material with known amounts and uncertainty.
b) Use a reference method with known uncertainty.
c) Spike a blank sample with the analyte.

Analyze a sample with the known true amounts at three different concentrations:

a) Close to the limit of quantitation
b) In the middle range
c) Close to the upper range

The sample should be processed through the entire analytical procedure, including sample preparation.

Calculate the deviation of the result obtained with the method to be validated with the true value. Compare the deviation with the criteria as specified in Table 1.

Precision of amounts (repeatability):

Inject solutions A, C, and E six times. Calculate the standard deviation of the measured amounts. Compare the results with those as specified in Table 1.

Intermediate precision:

Inject solutions A, C, and E on 15 working days. The analysis should be conducted by three different operators and three different columns should be used. Calculate the standard deviation of the measured amounts. Compare the results with those as specified in Table 1.

Limit of detection (LOD):

Prepare a standard solution with a concentration that is expected to be close to the detection limit. Inject the sample three times. Measure baseline noise, and signal height and determine signal/noise for each measurement. Use the formula:

$$\text{LOD (ng/L)} = \frac{3 \times \text{Signal height} \times \text{Standard amount (ng/L)}}{\text{Baseline noise}}$$

Average the results and compare with those specified in Table 1.

Limit of quantitation (LOQ):

Prepare six standard solutions with the amounts in the range from the expected limit of quantitation to 20 times this amount. Inject all samples six times and calculate the standard deviations of the amounts. Plot the standard deviations versus the amount. Take the standard deviation as specified in Table 1 and take the corresponding amount from the plot. Check if the LOQ meets the criteria as specified in Table 1.

8. Validation of Standard Methods

- Check the scope and performance criteria of the standard method.
- Check if the scope and performance criteria are within the scope of your analysis.
- Check the method's text for any evidence that the standard method has been validated.
- Check if the results from the standard match the requirements of your method.
- If either the scope of the standard method or the results differ from your criteria, or if there are no validation data available, the missing validation data should be generated.

Parameter	**Standard method**	**User's method**	**Comment**
Specificity Accuracy Repeatability Intermediate precision Reproducibility Limit of detection Limit of quantitation (at a standard deviation of xx %) Linearity Range			

9. Revalidation After Changes

The method should be revalidated after changing any of the following method parameters:

Change	Parameter to be validated
Concentration	Linearity, accuracy, recovery, precision
Delay volume of the HPLC pump	Selectivity (chromatographic separation)

10. Validation Report

The validation report should include the following:

- Summary
  A summary of the objective, and the scope and a statement that the results comply with the methods intended use as specified in Section 4.
- Method Authors
  This should include the name(s), addresses, and phone/fax numbers of the authors of the method.
- The principle of the methods
- Standards, reagents, materials, and equipment used for the experiments
- Procedure
- Calculations
- Validation results
- Critical points, if any
- Other comments, if any

Example #3: Testing Precision of Peak Retention Times and Areas of an HPLC System

The following is an example of an operating procedure for the testing of an HP 1050 Series HPLC system for the precision of peak areas and retention times. This is a proposal and starting point only and may need adaptation to different HPLC systems. There is no assurance expressed that the operating procedure will pass a regulatory inspection.

1. Scope

Testing the precision of peak areas and retention times of an HPLC system.

2. Purpose

The precision of peak areas and retention times are important characteristics for qualitative and quantitative measurements in HPLC. This operating procedure provides chromatographic conditions and key sequences to verify

these characteristics of a complete HPLC system, comprising an Autosampler, a Gradient Pump, and a Variable Wavelength Detector.

3. Frequency

The precision should be verified at least once a year or after the repair of one or more modules.

4. Instrumentation

a) Gradient HPLC Pump
b) Autosampler
c) Wavelength Detector
d) Data system for instrument control, data acquisition, and evaluation

5. Columns, Chemicals

a) Column: 100 mm × 4.6 mm Hypersil OD
b) Solvents: Water and Methanol, HPLC grade.
c) Sample: Isocratic standard sample (e.g., 0.15 wt.% dimethylphthalate, 0.15 wt.% diethylphthalate, 0.03 wt.% biphenyl, 0.03 wt.% o-terphenyl dissolved in methanol.)

6. Preparation of the Variable Wavelength Detector

a) Switch lamp ON.
b) Set the wavelength to 254 nm.
c) Set the response time to 1 SEC.

7. Preparation of the Pump

a) Prime the pump following the instrument operating manual.
b) Fill solvent reservoirs: A with water, B with water, C with methanol.
c) De-gas solvents following the instrument manual.
d) Set UPPER LIMIT to 400 (bar).
e) Set the FLOW rate to 3.00 ml/min.
f) Set the temperature of the column oven to 45ºC.
g) Set the solvent composition: A = off, B = 15%, C = 70% (channel A will be changed automatically according to %B and %C settings).
h) Set the STOP TIME to 5.00 minutes.
i) Switch pump ON.

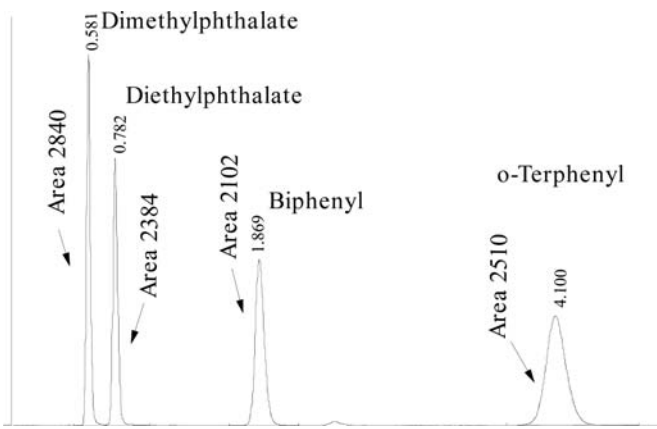
8. Preparation of the Autosampler

a) Make sure that the air pressure needed for the solenoid valves is about 5 bar.
b) Switch the autosampler on.
c) Put sample vial with isocratic sample into the vial tray, position number 10.
d) Set up vial numbers: FIRST 10, LAST 10.
e) Set the number of injections/vial to 6.
f) Set the injection volume to 10 µl.

9. Set Parameters for the Data System Following the Data Systems Operating Manual

10. Analysis of Isocratic Standard

a) When the baseline is stable, start the analyses.
b) As a result, 6 chromatograms similar to the figure below should be obtained (differences may occur in retention times and areas due to variations between different column batches and to variations in the concentration of the sample from batch to batch).



11. Acceptance

a) Calculate the precision of retention times and peak areas.

$$\text{RSD} = \frac{\sqrt{\frac{1}{n-1}\sum(x-\bar{x})^2}}{\bar{x}}100$$

where : n is the number of injections

x is area of retention time of peak

$$\text{Mean} = \bar{x} = \frac{1}{n}\sum x$$

b) The precision for the peak areas should be < 1.5 % RSD.
c) The precision for retention times should be < 0.5 % RSD.

12. Further Action

If the HPLC system does not fulfill the given specification, do the following:

a) Check the performance of the detector (noise and drift) using appropriate following the instrument operating manual.
b) Check whether the pump is leak-tight following the instrument operating manual.
c) Check whether the autosampler is leak-tight following the instrument operating manual.

If following these procedures does not result in an improvement, call the vendor's service.

13. Protocol Example for Results

Instrument identification
Serial number pump: ----------
Serial number autosampler : ----------
Serial number detector: ----------
System ID data system: ----------

Date: ----------

Results
Precision of peak areas: ---------- (spec < 1.5 % RSD)
Precision of retention times: ---------- (spec < 0.5 % RSD)

Comment:

Further actions (in case the equipment is out of specification)

Approvals

	Name	Signature	Date
Laboratory supervisor	----------	----------	----------
Test engineer	----------	----------	----------

Example #4: Retrospective Evaluation and Validation of Existing Computerized Analytical Systems

The following is an example of an operating procedure for the retrospective evaluation and validation of existing computerized analytical systems. This is a proposal and starting point only and may need adaptation to different HPLC systems. There is no assurance expressed that the operating procedure will pass a regulatory inspection.

1. Scope

Evaluation of existing computerized analytical systems retrospectively for past and current use and prospective validation for future use. The procedure is limited to systems purchased from a vendor.

2. Purpose

Regulatory agencies require computerized analytical systems used for the analysis and evaluation of critical data to be validated. Existing computerized systems in laboratories frequently have not been formally validated or their initial validation was not documented. The purpose of this operating procedure is to demonstrate whether such systems were operating as intended in the past, whether they are currently operating as intended, and whether they will operate as intended in the future.

3. Develop a Validation Plan

Define validation requirements. Define current system expectations; evaluate what was done in the past and what is planned for the future to meet these expectations. For content and details of the plan, follow Steps 4 to 7 of this operating procedure.

4. Describe and Define the System

a) Describe the purpose of the system.
b) List the equipment hardware.
   - — in-house identification number
   - — merchandising number or name
   - — manufacturer's name, address and phone number
   - — hardware serial number, firmware revision number
   - — date received in the laboratory
   - — date placed in service
   - — location
c) List all computer hardware.
   - — manufacturer's name
   - — model, serial number
   - — processor, coprocessor

  - — memory (RAM)
  - — graphics adapter
  - — hard disk
  - — interfaces
  - — network

d) List all software loaded on the computer software with product number, version number, and the name of the vendor.
  - — operating system, user interface
  - — canned standard software
  - — user specific application software, e.g., macros, with date and size

e) List accessories such as cables, spare parts, etc.
f) Find and review or develop system drawings.
g) Define operator requirements.
h) Define all required functions and operational limits of the modules and system as used for the current application.
  - — equipment hardware
  - — software and for system functions

i) Define physical and logical security requirements, e.g., physical or password access.

5. Collect Any Documentation Available

a) Reports from internal users on number and type of problems
b) Reports from external users on number and type of problems
c) Purchase orders
d) Certificates and specifications from the vendor
e) Information on what formulas are used for calculations
f) Operating procedures, for example, for basic operation, maintenance, calibration, and testing of the system
g) User manuals

6. Collect Information on System History

a) Installation reports
b) Information on acceptance testing
c) System failure reports
d) Equipment hardware and system maintenance logs
e) Maintenance records
f) Calibration records
g) Results of module and system performance checks
h) Any test reports
i) Records on operator qualifications

7. Evaluate Past and Current System Performance and Document Results

Evaluate information and documentation collected under Steps 5 and 6.

a) Check to see if documentation as collected under 5(f) and 5(g) is complete and up to date. For example, does the revision of the existing user manual comply with firmware and software revision numbers?
b) Check to see if there is evidence of software development validation. Qualification criteria are availability of type and number of documents listed under 5(d).
c) Check to see if the equipment (hardware) has been qualified for proper and up-to-date functions over the anticipated operating ranges as specified in 4(h). Generate a matrix with equipment functions as defined in 4(h) versus results of calibrations and performance checks as defined in 4(h).
d) Check to see if the computer system has been qualified for proper and up-to-date functions over the anticipated operating ranges as specified in 4(h). Generate a matrix with system functions as defined in 4(h) versus results of acceptance testing. Check if calculations made by the computer software have been verified.
e) Check to see if the computerized system is suitable for its intended use as specified in 4(h). Generate a matrix with performance requirements as defined in 4(h) versus results of system tests.
f) Check to see if the system is secure enough to meet the security requirement specifications as specified in 4(i). Check also if the security features have been verified sufficiently.
g) Check to see if the number and type of errors reported under 6(c) indicate continuous functioning of the system.
h) Check to see if the operators were/are qualified for their jobs.
i) Prepare an evaluation report. Make a statement on past and current validation status, whether the system is formally validated (if not, define what changes to the system are needed), and make proposals for further validation steps for future use of the system.

8. Prospective Validation for Future Use

a) Update or develop system description, user requirement specifications, operating ranges, user manuals, appropriate SOPs, and safety procedures as necessary.
b) Update or develop and implement a test and verification plan for the equipment. The plan should be developed to verify the performance of the various equipment parameters over the anticipated operating ranges and should include documented test procedures, expected results, and acceptance criteria. After the test phase a formal report that documents the results should be generated.
c) Update, develop, and implement an acceptance test plan for the computer system. Develop a test plan to exercise the various functions of the

computer system. Specify the functions to be tested, the purpose of the individual tests, the test steps or methodology, the expected results, and the acceptance criteria. Develop test cases and test data sets with known inputs and outputs for functional testing. Include test cases with normal data across the operating range, boundary testing and unusual cases (wrong nputs). After the test phase, a formal report that documents the results should be generated.

d) Update or develop and implement an operator qualification plan.
e) Update or develop and implement a preventive maintenance plan.
f) Update or develop and implement a calibration schedule and/or a performance verification schedule.
g) Update or develop and implement a procedure for annual system review. Update or develop and implement an error recording,
h) reporting, and remedial action plan.

9. Approvals

The validation plan, the system definition, the results of past and current evaluation, the prospective validation plan and test plans and results should be approved and signed by the user and the QA departments.

Appendix D

Books in the Area of Qualification and Validation

QUALITY ASSURANCE/QUALITY CONTROL

Quality in Chemical Measurements

- *Keywords*: Quality assurance, training, experiments to demonstrate Quality, uncertainty, traceability
- *Author*: N. Neidhardt and W. Wegscheider
- *Publisher*: Springer, 2000, ISBN 3-540-65994-3
- *Comment*: 176 pages. This book is based on presentations given at the 2nd EURACHEM Workshop on Current Issues in Teaching and Training. Includes a CD with course material of 15 experienced lecturers on over 300 slides in ppt format.

Analytical Chemistry in GMP Environment

- *Keywords*: GMP, pharmaceutical laboratories, drug development, statistics
- *Author*: J.M. Miller and J.B. Crowther
- *Publisher*: Wiley, 2000, ISBN 0-471-31431-5
- *Comment*: 486 pages. Describes the drug development process and as it relates to analytical chemistry. Includes appendices for unifying terms, symbols, and procedural information.

Quality Assurance of Chemical Measurements

- *Keywords*: Quality assurance, statistics, sampling, calibration, validation
- *Author*: John Keenan Taylor
- *Publisher*: CRC Press, Inc, 1987, ISBN: 0-87371-097-5
- *Comment*: 328 pages. Published in 1987 but still considered to be the reference book for Quality assurance of chemical measurements.

Guidelines for Laboratory Quality Auditing

- *Keywords*: Quality assurance, audits, accreditation, OECD-GLP, US-FDA GLP
- *Author*s: Donald C. Singer and Ronald P. Upton
- *Publisher*: ASQC Quality Press, Marcel Dekker, 1993, ISBN: 0-8247-8784-6
- *Comment*: 411 pages with 43 pages of text and over 300 pages with appendices on EPA's, FDA's, and the OECD Good Laboratory Practice Regulations.

Accreditation and Quality Assurance in Analytical Chemistry

- *Keywords*: Quality assurance, accreditation, statistics, sampling, method validation, traceability, reference material, accreditation versus GLP, EURACHEM, U.S. EPA
- *Editor*: Helmut Günzler
- *Publisher*: Springer-Verlag, 1996, ISBN: 3-540-60103-1
- *Comment*: 265 pages. Multi-author book with very comprehensive and detailed information on the individual topics.

Laboratory Quality Assurance System

- *Keywords*: Quality assurance, procedures, accreditation, laboratory infrastructure
- *Editor*: T. A. Ratliff
- *Publisher*: Wiley, 2003, Third edition, ISBN: 0-471-26918-2
- *Comment*: 236 pages. Includes chapters on laboratory infrastructure, chain-of-custody procedures, preventive maintenance, audit checklists.

Quality Assurance for Analytical Laboratories

- *Keywords*: Quality assurance, accreditation, statistics, GLP, reference material
- *Author*: M. Parkany
- *Publisher*: Royal Society of Chemistry, 1993, ISBN: 0-85186-705-7
- *Comment*: 197 pages. For self audits in preparation for ISO 9000 in laboratories, includes excellent chapter on people motivation.

Quality Assurance and TQM for Analytical Laboratories

- *Keywords*: Quality assurance, accreditation, statistics, quality audits, reference material, method validation
- *Editor*: M. Parkany
- *Publisher*: Royal Society of Chemistry, 1995, ISBN: 0854047603
- *Comment*: 287 pages

Quality in the Analytical Chemistry Laboratory

- *Keywords*: Quality assurance, sampling, method selection, equipment, reference material, statistics, reporting, uncertainty, costs
- *Coordinating Author*: E.Prichard.
- *Other Author*s: Neil T. Crosby, John A. Day, William A. Hardcastle, David G. Holcombe and Ric D. Treble
- *Publisher*: John Wiley & Sons, 1997, ISBN: 0-471-95470-5
- *Comment*: 307 pages. Very practical book with many checklists that help to implement a quality system.

Quality Assurance Principles for Analytical Laboratories

- *Keywords*: Quality assurance, statistics, control charts, people qualification, equipment, sample handling, sampling, control samples, audits, safety, accreditation, quality manual
- *Author*: Frederick M. Garfield
- *Publisher*: AOAC International, 3rd edition, 2000, ISBN: 0-935584-46-3
- *Comment*: Comprehensive information on all aspects of QA in a chemical laboratory. Excellent chapter on using quality control charts. Good summary tables of equipment qualification.

Quality Control in Analytical Chemistry

- *Keywords*: Quality assurance, sampling, data processing, costs
- *Author*s: G. Kateman and L. Buydens
- *Publisher*: John Wiley & Sons, Inc, 1993, ISBN: 0-471-55777-3
- *Comment*: Second edition with 317 pages, includes large chapters on sample handling, sampling, and on data handling.

Quality Planning, Control, and Improvement in Research and Development

- *Keywords*: Quality control, statistical process control, research quality, quality planning, software quality assurance, improvements
- *Author*: G. W. Roberts
- *Publisher*: Marcel Dekker, 1995, ISBN: 0-8247-9585-7
- *Comment*: 317 pages. Offers valuable guidance for the planning and balancing of technology portfolio; also presents customer survey for monitoring a laboratory's effectiveness; includes appendices that research effectiveness, quality planning, and control.

Writing the Laboratory Notebook

- *Keywords*: Notebook, GLP, GMP
- *Author*: Howard M. Kanare

- *Publisher*: American Chemical Society, 1985, ISBN: 0-8412-0906-5
- *Comment*: 145 pages. Detailed information in writing a laboratory paper notebook.

LABORATORY ACCREDITATION AND ISO 9000

Laboratory Accreditation and Data Certification

- *Keywords*: Accreditation, certification, data, US-EPA
- *Author*s: Carla H. Dempsy and J.D. Petty
- *Publisher*: Lewis *Publisher*, 1991, ISBN: 0-87371-291-9
- *Comment*: 239 pages. Description of accreditation schemes. The book presents a system for laboratory accreditation in conjunction with data certification.

Food and Drink Laboratory Accreditation

- *Keywords*: Quality assurance, accreditation, NAMAS, audits
- *Author*s: Sandra Wilson and Geoff Weir
- *Publisher*: Chapmann & Hall, 1995, ISBN: 0-412-59920-1
- *Comment*: 262 pages. Useful book on how develop, get, and maintain accreditation. Examples of a NAMAS quality manuals help with implementation.

The Memory Jogger 9000/2000: A Pocket Guide to Implementing the ISO 9001 Quality Systems Standard Based on ANSI/ISO/ASQ Q9001-2000

- *Keywords*: ISO 9001:2000 Series, implementation
- *Author*: R. W. Peach, B. Peach and Diane S. Ritter
- *Publisher*: Goal/QPC, 2000, ISBN: 157681032
- *Comment*: 177 pages

The Quality Audit For ISO 9001:2000: A Practical Guide

- *Keywords*: ISO 9001:2000, auditing, quality system
- *Author*: David Wealleans
- *Publisher*: Gower Publishing Ltd, 2005, ISBN: 0566085984
- *Comment*: 299 pages, second edition with focus on ISO 9001:2000

EQUIPMENT QUALIFICATION AND COMPUTER SYSTEM VALIDATION

Validation of Computerized Analytical and Networked Systems

- *Keywords*: validation, computers, national/international regulations, spreadsheets, networks, pharmaceutical industry
- *Author*: Ludwig Huber

- *Publisher*: Interpharm/CRC, 2002, ISBN 1-57491-133-3
- *Comment*: 228 pages. Readers will learn what is required for validation of computerized analytical and networked systems and how to do it right the first time. Includes many checklists and SOPs for easy implementation.

Validation of Chromatography Data Systems---Meeting Business and Regulatory Requirements

- *Keywords*: validation, chromatography, data systems, computer validation, life cycle
- *Author*: R D McDowall
- *Publisher*: RSC Publishing, 2005, ISBN 0 85404 969 X
- *Comment*: 266 pages. Includes basics of computer validation, for the chromatographer working in analytical laboratories in the regulated pharmaceutical, contract research, biotechnology, and medical device industries.

Laboratory Systems Validation Testing and Practice

- *Keywords*: laboratory systems, equipment hardware, software, computer systems, HPLC, UV spectrometers
- *Author*: Paul Coombes
- *Publisher*: Davis Horwood International Publishing, 2002, ISBN: 1-930114-48-6
- *Comment*: 150 pages. Gives detailed examples on how to test analytical equipment such as HPLC, LC/MS Systems, GCs, and UV spectrometers.

Validating Automated Manufacturing and Laboratory Applications

- *Keywords*: validation, computers, international regulations, pharmaceutical industry, manufacturing
- *Editor/Author*s: Guy Wingate, Multiple authors
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1995, ISBN: 0-57491-037-X
- *Comment*: 564 pages, includes 15 practical case studies on 270 pages

Computer Validation -- The 100 Worst Mistakes You Can Make

- *Keywords*: computers, software, validation
- *Author*: T. Follet
- *Publisher*: CVSI Press, 2003, ISBN: 0-9705456-1-4
- *Comment*: 232 pages. The book lists 100 common mistakes and gives recommendations on how to avoid them.

Computer Infrastructure Qualification for FDA Regulated Industries

- *Keywords*: Computers, networks, qualification, life cycle, risk analysis
- *Author*: O. Lopez

- *Publisher*: Davis Healthcare International Publishing, 2006, ISBN: 1-933722-00-2
- *Comment*: 262 pages. Includes examples for qualification steps.

Good Computer Validation Practices: Common Sense Implementation

- *Keywords*: Validation, computers, SOPs, international regulations, life cycle, pharmaceutical industry
- *Author*s: Teri Stokes, Ronald C. Branning, Kenneth G. Chapman, Heinrich Hambloch and Anthony J. Trill
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1994, ISBN: 0-935184-55-4
- *Comment*: 324 pages. Written by a group of international experts on computer validation. Covers aspects of new and existing systems.

METHOD VALIDATION/STATISTICS/MEASUREMENT UNCERTAINTY

Analytical Method Validation and Instrument Performance Verification

- *Keywords*: Method validation, analytical instruments, qualification, HPLC, UV, MS
- *Author*: C.C. Chan, H. Lam, Y.C. Lee and X.-M. Zhang
- *Publisher*: Wiley, 2004, ISBN 0-471-25953-5
- *Comment*: 304 pages. Multiple authors cover a wide range of validation activities.

Method Validation in Pharmaceutical Analysis: A Guide to Best Practice

- *Keywords*: Method validation, equipment qualification
- *Author*s: Joachim Ermer (*Editor*), John H. McB. Miller (*Editor*)
- *Publisher*: Wiley, 2005, ISBN: 0-8504-482-5
- *Comment*: 418 pages. Multiple authors, lots of details on method validation.

Valid Analytical Methods and Procedures

- *Keywords*: Method validation, transfer, laboratories
- *Author*: C. Burgess
- *Publisher*: Springer, 2000, ISBN: 0-8504-482-5
- *Comment*: 87 pages. Focus on selecting and defining robust laboratory procedures; includes examples.

Development and Validation of Analytical Methods

- *Keywords*: Regulations, pharmaceutical, robotics, out of specification situations, dissolution studies, biological samples
- *Editor*s: Christopher M. Riley and Thomas W. Rosanske

- *Publisher*: Pergamon Press, 1996, ISBN: 0-08042792-8
- *Comment*: 352 pages. The book includes an up-to-date review on international regulations and guidelines related to the topic. The chapter on interpretation of the cGMP issues contained in the U.S. Court's Ruling in the *United States v. Barr Laboratories* is extremely valuable for pharmaceutical QA/QC laboratories. Also the chapter on validation of methods for biological samples is very useful and provides detailed instructions related to the topic.

Analytical Method Development and Validation

- *Keywords*: Method validation, pharmaceutical, ICH, FDA
- *Author*s: Michael E. Swartz and Ira Krull
- *Publisher*: Marcel Dekker 1997, ISBN: 0-8247-0115-1
- *Comment*: 92 pages

Measurement Uncertainty in Chemical Analysis

- *Keywords*: Analytical laboratory, measurement uncertainty, metrology, reference material
- *Author*s: P. DeBievre, H. Guenzler and others
- *Publisher*: Springer, 2002, ISBN: 3-540-43990-0
- *Comment*: 292 pages. This book collects 20 papers on the topic, mostly published from 1999-2002 in the journal "Accreditation and Quality Assurance."

REGULATIONS AND GUIDELINES - GLP, GALP, cGMP, GCP, ETC.

Good Pharmaceutical Manufacturing Practice

- *Keywords*: Regulations, validation, pharmaceutical, documentation
- *Author*: J. Sharp
- *Publisher*: CRC Press, 2005, ISBN: 08493-1994-3
- *Comment*: 503 pages. Very detailed regulatory background from U.S. FDA and Europe, recommendations for implementation, reference book for GMP.

How to Practice GLP

- *Keywords*: Regulations, GLP, sampling, statistical quality control, good analytical practice
- *Author*: P.P. Sharma
- *Publisher*: Vandana Publications, ISBN: 81-900892-1-8
- *Comment*: 410 pages, includes 21 CFR 58 text, has recommendations to implement good analytical practices beyond GLP regulations.

Implementing International Good Practices

- *Keywords*: Regulations, international, GMP, GLP, GCP, OECD
- *Author*: Nigel J. Dent
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1993, ISBN: 0-935184-44-9
- *Comment*: 284 pages. Very good overview about worldwide Good Laboratory and Good Clinical Practice regulations. Focus on OECD GLPs, GMP in Scandinavia, GLP in Japan, GCPs in US and Europe, approaches to implementation

FDA-SPEAK; The Interpharm Glossary of Acronyms and Regulatory Terms

- *Keywords*: Regulations, GMP, GLP, glossary
- *Author*: Dean E. Snyder
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1992, ISBN: 0-935184-30-9
- *Comment*: 267 pages. A common language on aspects of good practices and validation is very important for a good understanding of the topics. This book provides the terminology of the U.S. FDA and is recommended for those who have involvement with the U.S. FDA. Includes also organization charts, addresses. and phone numbers of the U.S. FDA.

Good Laboratory Practice and Current Good Manufacturing Practice

- *Keywords*: GLP, cGMP, HPLC, GC, MS, CE, UV-Vis
- *Author*: Ludwig Huber
- *Publisher*: Agilent Technologies, 2004, Publication number: 5968-6193E
- *Comment*: 152 pages. Provides summary of basics of GLP and cGMP and its impact on analyses with HPLC, GC, MS, CE, and UV-Vis spectroscopy.

GCP Quality Audit Manual

- *Keywords*: GCP, audits
- *Author*: James E. Sayre
- *Publisher*: Interpharm Press, Buffalo Grove, IL, Buffalo Grove, IL, 1990, ISBN 0-935184-56-2
- *Comment*: Binder format, 60 pages text, 56 pages audit checklists, 173 pages regulatory text.

International GLPs

- *Keywords*: GLP, regulations, international, memorandum of understandings
- *Author*s: Robert S. DeWoskin and Stefanie M. Taulbee
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1993, ISBN: 0-935184-42-2

- *Comment*: 452 pages, binder format. Side-by-side comparison of the most well-known national and international GLP standards. Includes full text of most GLPs: U.S. EPA; U.S. FDA; OECD; Japanese Ministry of Health and Welfare (MHW); Japanese Ministry of Agriculture, Forestry and Fisheries; Japanese Ministry of International Trade and Industry. It also includes text of many memorandums of understandings (MOU).

International Drug GMPs

- *Keywords*: GMP, regulations, international
- *Author*: Michael H. Anisfield
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 1993, ISBN: 0-935184-17-1
- *Comment*: More than 500 pages, binder format. Summary of worldwide Good Manufacturing Requirements. Summary of countries performing international GMP inspections. Texts of international conventions and requirements (WHO, Asian, EU, PIC-GMP, PIC-Bulk). Text of more than 20 national GMPs. Listing of national regulatory agencies responsible for drug manufacturing regulations.

Good Laboratory Practice Regulations

- *Keywords*: GLP, U.S. FDA and international regulations
- *Author*: Allen F. Hirsch
- *Publisher*: ASQC Quality Press, Marcel Dekker, 1989, ISBN: 0-8247-8101-5
- *Comment*: 234 pages. Already published in 1989 it is still one of the reference book on the basics of GLP. Includes many practical examples for implementation.

Good Laboratory Practice Regulations

- *Keywords*: GLP, U.S. FDA, and international regulations
- *Author*s: S. Weinberg, G. James, L. Robinson and others
- *Publisher*: Marcel Dekker, 2002, ISBN: 0-8247-0891-1
- *Comment*: 244 pages. Overlaps with the book from A.F. Hirsch. Includes chapter on good automated laboratory practices.

Good Laboratory Practice Standards

- *Keywords*: GLP, SOPs, field studies, computer validation, U.S. EPA
- *Author*s: Willa Y. Garner, Maureen S. Barge and James P. Ussary
- *Publisher*: American Chemical Society, 1992, ISBN: 0-8412-2192-8
- *Comment*: 571 pages. Very detailed book on implementing GLPs. Focus on EPA-GLPs. Includes appendices with text of GLP standards and standard forms for submitting data to the U.S. EPA and a question/answer section.

PHARMACEUTICAL

Quality Assurance for Biopharmaceuticals

- *Keywords*: Quality assurance, regulations, GMP, biopharmaceutical, sampling, method validation
- *Author*: Jean F. Huxsoll
- *Publisher*: John Wiley & Sons, 1994, ISBN: 0-471-03656-0
- *Comment*: 206 pages. Tailored to the biopharmaceutical manufacturing process.

Qualification and Validation in Pharmaceutical Manufacture

- *Keywords*: Quality assurance, regulations, GMP, biopharmaceutical, sampling, method validation
- *Author*s: Seminar speakers of a seminar held at Dublin, 1994
- *Publisher*: Published by the Secretariat to the Convention for the Mutual Recognition of Inspections in respect of the Manufacture of Pharmaceutical Products (EFTA Secretariat 9-11 rue de Varembe, CH-1211 Geneva 20), 1994
- *Comment*: 287 pages. Includes useful information on regulatory requirements and solutions as practiced in the pharmaceutical industry. Some chapters are very detailed. Good chapter on 'how much validation is enough?'

Documentation Basics; That Support Good Manufacturing Practices

- *Keywords*: GMP, documentation
- *Author*: Carol DeSain
- *Publisher*: Aster Publishing Corporation, 1993, ISBN: 0-943330-30-0
- *Comment*: 88 pages. Describes documentation requirements for cGMP and gives recommendations on who writes what. Includes many forms for easy implementation.

Training for the Healthcare Manufacturing Industries: Tools and Techniques to Improve Performance

- *Keywords*: Pharmaceutical, people, training
- *Author*: James L. Vesper
- *Publisher*: Interpharm Press, Buffalo Grove, IL, 01993, ISBN: 0-935184-43-0
- *Comment*: 413 pages. Examines topics related to training, adult learning, human performance, and new training technologies. Includes evaluation forms.

Appendix E

References

1. US Food and Drug Administration. Current good manufacturing practice for finished pharmaceuticals. Washington, DC: Dept of Health and Human Services, Center for Drug Evaluation and Research. 2005. CFR publication 21:211.
2. US Food and Drug Administration. Guidance for Industry: Analytical Procedures and Methods Validation; Chemistry, Manufacturing, and Controls and Documentation (Draft). Rockville, MD: Center for Biologics Evaluation and Research; 2000.
3. US Food and Drug Administration. Guidance for Industry: Bioanalytical Method Validation. Washington, DC: Dept of Health and Human Services, Center for Drug Evaluation and Research. 2001.
4. ICH. Guidance for Industry: Validation of Analytical Procedures: Definitions and Terminology, Q2A. Geneva Switzerland. 1996.
5. ICH. Guidance for Industry: Validation of Analytical Procedures: Methodology. Geneva Switzerland. Q2B. 1996.
6. US Pharmacopeia, USP Chapter 1058: Analytical Instrument Qualification (Draft). Rockville MD. Pharmaceutical Forum 2006; 32:6.
7. GAMP Good Automated Manufacturing Practice. Good Practices Guide: Validation of Laboratory Computerized Systems, 2005, available through www.ispe.org.
8. US Environmental Protection Agency. Guidance for methods development and methods validation for the Resource Conservation and Recovery Act (RCRA) Program, Washington, D.C. 1995 at http://www.epa.gov/sw-846/pdfs/methdev.pdf.
9. AOAC. Peer-Verified Methods Program: Manual on Policies and Procedures, Arlington, VA. 1998. http://www.aoac.org/vmeth/PVM.pdf.
10. ISO. Control Charts-General Guide and Introduction. Guide 7870:1993.
11. ISO. Control Charts for Arithmetic Average with Warning Limits. Guide 7873:1993.

12. ISO. Acceptance Control Charts. Guide 7966:1993.
13. ISO. Shewhart Control Charts. Guide 8258:1991.
14. ISO. Calibration of Chemical Analysis and Use of Certified Reference Materials. 1997. Guide 32.
15. ISO. Use of Certified Reference Material. 1989. Guide 33.
16. ISO. Certification of Reference Materials-General and Statistical Principles. 2006. Guide 35.
17. European Commission. Annex 15 to the EU Guide to Good Manufacturing Practice: Qualification and Validation. Brussels Belgium. 2001.
18. Sharp J, Validation - How Much Validation is Required, in Proceedings: Convention of the Mutual Recognition of Inspections in Respect of the Manufacture, Qualification and Validation in Pharmaceutical Manufacture, Dublin, 1994:266.
19. Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S). Aide Memoire: Quality control Laboratories. Geneva Switzerland. 2005 at http://www.picscheme.org/.
20. Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S). Aide Memoire: Inspection of Biotechnology Manufacturers. Geneva Switzerland. 2005.at http://www.picscheme.org/.
21. Pharmaceutical Inspection Convention/Cooperation Scheme (PIC/S). Guidance: Good Practices for Computerised Systems in Regulated "GXP" Environments. Geneva Switzerland. 2003 at http://www.picscheme.org/.
22. US Food and Drug Administration. Guide for Inspections of Pharmaceutical Quality Control Laboratories, Rockville, MD. 1993.
23. US Food and Drug Administration. Biotechnology Inspection Guide: Reference Material and Training Aids, Rockville, MD. 1991.
24. US Food and Drug Administration, Guide to Inspections of Foreign Pharmaceutical Manufacturers. Rockville, MD. 1993.
25. US Food and Drug Administration. Compliance Program Guidance Manual: Drug Manufacturer Inspections. Rockville, MD. 2002.
26. US Food and Drug Administration. Industry Guide: Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production. Rockville, MD. 2006.
27. US Food and Drug Administration. Industry Guide: Quality Systems Approach to Pharmaceutical CGMP Regulations. Rockville, MD. 2006.
28. US Pharmacopeia, USP Chapter 1225: Validation of Compendial Methods. United States Pharmacopeia 30, National Formulary 25. Rockville MD. 2007.
29. Freeman M, Leng M, Morrison D, et al., Position Paper: Qualification of Analytical Equipment. Pharm. Tech. Europe. 1995. 40–46.

30. Bedson P, Sargent M. The Development and Application of Guidance on Equipment Qualification of Analytical Instruments. Accred. Qual. Assur. 1996. 1 (6):265–274.
31. CITAC/EURACHEM Working Group. International Guide to Quality in Analytical Chemistry: An Aid to Accreditation, Teddington. 2002.
32. US Food and Drug Administration. Good Laboratory Practice Regulations for Non-clinical Studies. Rockville, MD, 1979. CFR Publication 21:58.
33. US Environmental Protection Agency. Federal Insecticide, Fungicide and Rodenticide Act (FIFRA): Good Laboratory Practice Standards. Federal Register 48 (230):53946–53969. 1983.
34. US Environmental Protection Agency. Toxic Substance Control Act (TSCA): Good Laboratory Practice Standards. Federal Register 54 (158):34034–34052; Aug. 17, 1989. CFR Publication 40:792.
35. OECD. Final Report of the Group of Experts on Good Laboratory Practice: Good Laboratory Practice in the Testing of Chemicals. Geneva Switzerland. 1982. (out of print).
36. OECD. GLP Consensus Document Environment Monograph No. 45: The OECD Principles of Good Laboratory Practice. Paris. 1998.
37. European Union. The harmonization of Laws, Regulations and Administrative Provisions to the Application of the Principles of Good Laboratory Practice and the Verification of their Application for Tests on Chemical Substances. Council Directive 2004/10/EC. 2004 at http://europa.eu/scadplus/leg/en/lvb/l21254.htm.
38. European Union. Good Laboratory Practice: Inspection and Verification of Laboratory Studies on all Chemicals. Council Directive 2004/9/EC. 2004. http://europa.eu/scadplus/leg/en/lvb/l21255.htm.
39. European Commission. The Rules Governing Medicinal Products in the European Union: Good Manufacturing Practices. Vol. 4. 2003. http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev4.htm.
40. Pharmaceutical Inspection Convention/cooperation Scheme (PIC/S). Guide to Good Manufacturing Practice for Medicinal Products. Geneva Switzerland. 2006.
41. European Commission. Annex 11 to the EU Guide to Good Manufacturing Practice: Computerized Systems. Brussels Belgium. 1993.
42. United States Food and Drug Administration (FDA), Electronic Records; Electronic Signatures. Rockville, MD. CFR publication 21:11. 1997.
43. Huber L, Primer: 21 CFR Part 11 - Electronic Records and Electronic Signatures. Labcompliance. Oberkirch Germany. 2005.
44. ICH. Second International Conference on Harmonization: Closing Report on the Status of Tripartite Harmonization Initiatives. Orlando, FL. 1993.

45. ICH. Guidance for Industry: Regulatory Acceptance of Analytical Procedures and/or Acceptance Criteria (RAAPAC). Q4B. Geneva Switzerland. 2006.
46. ICH, Guidance for Industry Stability Testing of New Drug Substances and Products. Q1A(R2): 2003.
47. ICH. Guidance for Industry Impurities in New Drug Substances (Revised). Q3A(R2). Geneva Switzerland. 2006.
48. ICH. Guidance for Industry Impurities in New Drug Products (Revised). Q3B(R2). Geneva Switzerland. 2006.
49. ICH. Guidance for Industry: Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients. Q7A. Geneva Switzerland. 2000.
50. ICH. Guidance for Industry: Quality Risk Management. Q9. Geneva Switzerland. 2005.
51. US Pharmacopeia . USP Chapter 621: Chromatography. United States Pharmacopeia 30, National Formulary 25, Rockville MD. 2007.
52. ISO. 9000 Standards Compendium: Quality Management. Geneva Switzerland. 2000.
53. ISO. Standard 17025: General Requirements for the Competence of Testing and Calibration Laboratories. Geneva Switzerland. 2005.
54. Bedson P, Rudd D. The Development and Application of Guidance on EQ of Analytical Instruments: High performance Liquid Chromatography. Accred. Qual. Assur. 4:56–62. 1999.
55. Labcompliance. Master Plan: Equipment Validation. Oberkirch Germany. 2005.
56. US Food and Drug Administration. General Principles of Validation, Rockville, MD., 1987.
57. World Health Organization. Good Practices for the Manufacture and Quality Control of Drugs, International Drug GMPs, Buffalo Grove, IL., Interpharm Press, Inc., 1993.
58. OECD. GLP Consensus Document 10: The Application of the Principles of GLP to Computerized Systems. Environment Monograph No. 116. Paris. 1995.
59. Chapman K.G. A History of Validation in the United States, Part I, Pharm. Tech. 1991:82–96.
60. ISO. General Terms, Their Definitions Concerning Standardization and Related activities. Geneva Switzerland. 1991. Guide 2.
61. GAMP Good Automated Manufacturing Practice. Guide for Validation of Automated Systems in Pharmaceutical Manufacture, Brussels Belgium. 2001. available through www.ispe.org
62. US Food and Drug Administration. Pharmaceutical GMPs for the 21st Century: A Risk-Based Approach. Rockville MD. 2002 at www.fda.gov/oc/guidance/gmp.html.
63. US Food and Drug Administration. Guidance for Industry and FDA Staff: General Principal of Software Validation. Rockville MD. 2002.

64. US Food and Drug Administration. Guidance for Industry: Part 11, Electronic Records; Electronic Signatures, Scope and Applications. Rockville MD. 2003.
65. National Institute of Information Technology. Risk Management Guide for Information Technology System. Washington D.C.. 2001. NIST Publication 800-30.
66. Murray J. Computer System Validation Conference: Part 11 – Electronic Records, Electronic Signatures. Institute of Validation and Technology. Arlington VA. 2004.
67. Labcompliance. Master Plan: Risk Management. Oberkirch Germany. 2007.
68. Mollah H. Risk Analysis and Process Validation, BioProcess International, 2 (9). 2004:28–38
69. ISO. Standard 14971:2000 - Medical devices - Application of Risk Management to Medical Devices. Geneva Switzerland. 2000.
70. GAMP Good Automated Manufacturing Practice. Good Practices Guide: A Risk Based Approach to Compliant Electronic Records and Signatures. Brussels Belgium. 2005. Available through www.ispe.org.
71. PMA's Computer System Validation Committee. Validation Concepts for Computer Systems Used in the Manufacture of Drug Products, Pharm. Tech. 10 (5):24–34. 1986.
72. ISO. Control Charts - General Guide and Introduction, Geneva Switzerland. Guide 7870:1993.
73. Huber L, Validation of Computerized Analytical and Networked Systems. Interpharm/CRC. 2002.
74. Labcompliance. Master Plan: Computer System Validation. Oberkirch Germany. 2005.
75. Shah V.P. et al. Analytical Methods Validation: Bioavailability, Bioequivalence and Pharmacokinetic Studies. Pharm. Res. 9:588–592. 1992.
76. Hokanson G.C., A Life Cycle Approach to the Validation of Analytical Methods during Pharmaceutical Product Development, Part I: The Initial Validation Process. Pharm. Tech., Sept. 1994: 118–130.
77. Hokanson G.C., Life Cycle Approach to the Validation of Analytical Methods during Pharmaceutical Product Development, Part II: Changes and the Need for Additional Validation, Pharm. Tech., Oct. 1994: 92–100.
78. Green J.M. A Practical Guide to Analytical Method Validation. Anal. Chem. News & Features 1996; 1:305A–309A.
79. Renger B, Jehle H, Fischer M, et al. Validation of Analytical Procedures in Pharmaceutical Analytical Chemistry: HPTLC Assay of Theophylline in an Effervescent Tablet. J. Planar Chrom. 1995; 8:269–278.
80. Wegscheider W, Validation of Analytical Methods, In: Accreditation and Quality Assurance in Analytical Chemistry ed. H. Guenzler. Springer Verlag, Berlin, 1996:135:158.

81. Seno S, Ohtake S and Kohno H. Analytical validation in practice at a quality control laboratory in the Japanese pharmaceutical industry, Accred. Qual. Assur. 1997:140–145.
82. Winslow P.A., Meyer R.F. Defining a Master Plan for the Validation of Analytical Methods, J. Validation Technology, 1997: 361–367.
83. Breaux J, Jones K, Boulas P, Understanding and Implementing Efficient Analytical Methods Development and Validation Pharm. Tech., Analytical Technology and Testing. 2003:6–13.
84. Krause S.O. A Guide for Testing Biopharmaceuticals, Part II: Acceptance Criteria and Analytical Method Maintenance. Pharm. Tech. Europe 2006; 18(6):29–38.
85. Vessman J, Selectivity or Specificity? Validation of Analytical Methods from the Perspective of an Analytical Chemist in the Pharmaceutical Industry, J. Pharm & Biomed Analysis 1996; 14:867–869.
86. Huber L, George S. Diode-array Detection in High-performance Liquid Chromatography. Marcel Dekker, New York. 1993.
87. EURACHEM. A Laboratory Guide to Method Validation and Related Topics: The Fitness for Purpose of Analytical Methods. Teddington. 1998.
88. ISO. Guide to the Expression of Uncertainty in Measurement. Geneva Switzerland. Switzerland, 1995. Guide 98
89. EURACHEM, Quantifying uncertainty in analytical measurement, ISBN 0-948926-08-2, Teddington, UK (1995).
90. US Food and Drug Administration. Warning Letters Letters, CDER Freedom of Information Office. Rockville MD, Ongoing sorted by month. at http://www.fda.gov/cder/warn/index.htm.
91. Lanese, J. Handling Out-of-Specification Results: A Current FDA View. Journal of cGMP Compliance 2000. 4(3)45–49.
92. Huber L. Preventing Out-of-Specification (OOS) Situations Caused by Laboratory Errors. Journal of GxP Compliance 2001; 6:24–31.
93. Huber L, Primer: Primer: Managing OOS, Failure Investigations and Corrective and preventive Action Plans, Labcompliance, Oberkich. 2007.
94. Bodea G, What Companies Should Know and Consider when Designing a CAPA System, Journal of GXP Compliance 2005; 9:58–66.
95. Bodea G, How to Set Up A CAPA Program From Scratch: Part II. Journal of GXP Compliance 2005; 10:48–68.
96. ISO. Terms and Definitions Used in Connection with Reference Materials. Geneva Switzerland. 1992. Guide 30.
97. Pan X. Hierarchy of Reference Materials Certified for Chemical Composition. Metrologia 1997; 34:35–39
98. Labcompliance. Audio Seminars. Oberkirch Germany. 2007 at http://www.labcompliance.com/seminars/audio.

99. ISO. Proficiency Testing by Interlaboratory Comparisons - Part 1: Development and Operation of Proficiency Testing Schemes. Geneva Switzerland. 1997. Guide 43-1.
100. ISO IEC: Proficiency Testing by Interlaboratory Comparisons - Part 2: Selection and Use of Proficiency Testing Schemes by Laboratory Accreditation Bodies. Geneva Switzerland. 1997. Guide 43-2.
101. Patey A.L. The Food Analysis Performance Assessment Scheme (FAPAS), The VAM Bulletin 1994; 11:12–13.
102. FAPAS. Food Analysis Performance Assessment Scheme (FAPAS) Protocol for the Analysis and Organization of Data. York UK, 2002. at http://www.fapas.com/pdfpub/FAPASProtocol.pdf.
103. Thompson M., Ellison S. and Wood R., International harmonized protocol for proficiency testing of chemical analytical laboratories, Pure Appl. Chem 2006., 78 (1):145–196 at http://www.iupac.org/publications/pac/2006/pdf/7801x0145.pdf.
104. Labcompliance. US Food and Drug Administration Warning Letters. Oberkirch Germany. 2007. at http://www.fdawarningletters.com.
105. Savage T.S. Laboratory Controls and Compliance Conference: Laboratory GMPs and Inspectional Issues - An FDA Perspective. Institute of Validation and Technology. Alexandria VA. 2006.
106. Olver M. Equipment Qualification and System Validation Conference: Equipment and Instrument Validation for Manufacturing and Laboratories. Institute of Validation and Technology Amsterdam Netherlands. 2006.
107. US Food and Drug Administration. Quality System Regulation. Rockville MD. 1996. CFR publication 21:820.
108. Furman W.B., Layloff T.P. and Tetzlaff R.F., Validation of Computerized Liquid, Chromatographic Systems, J. AOAC Intern. 1994. 77 (5), 1314–1318.

Index

Pharmaceutical Science

about the book...

This ***Second Edition*** discusses ways to improve pharmaceutical product quality while achieving compliance with global regulatory standards. This title serves as a complete source to the subject with comprehensive step-by-step instructions, practical recommendations, standard operating procedures (SOPs), checklists, templates, and graphics for easy incorporation in a laboratory, and explains how to develop and implement a validation strategy for routine, nonroutine, and standard analytical methods, covering the entire equipment, hardware, and software qualification process. It also provides guidance on qualification of certified standards, in-house reference materials, and people qualification, as well as internal and third party laboratory audits and inspections.

A practical source for understanding and managing laboratory validation and qualification processes, this guide incorporates new chapters on risk-based validation and qualification and action plans for laboratories…provides complete coverage of regulations and quality standards, including the new FDA 21 CRF Part 11 standard, ISO Standard 17025, and all major international standards…includes several appendices presenting detailed real world case studies, testing procedures, and a glossary.

about the author...

LUDWIG HUBER is Worldwide Compliance Fellow at Agilent Technologies, Waldbronn, Germany. Dr. Huber is the author of several books and published over 100 peer reviewed papers focused on validation, compliance, and 21 CFR Part 11. He is the editor of **www.labcompliance.com** and was a member of the PDA Task Force on 21 CFR Part 11. Dr. Huber received his Ph.D. in Chemical Engineering, University of Karlsruhe, Germany.

Printed in the United States of America

DK8267

ISBN 978-084938267-3

9 780849 382673 90000

informa
healthcare
www.informahealthcare.com

52 Vanderbilt Avenue
New York, NY 10017

Telephone House
69-77 Paul Street
London EC2A 4LQ, UK