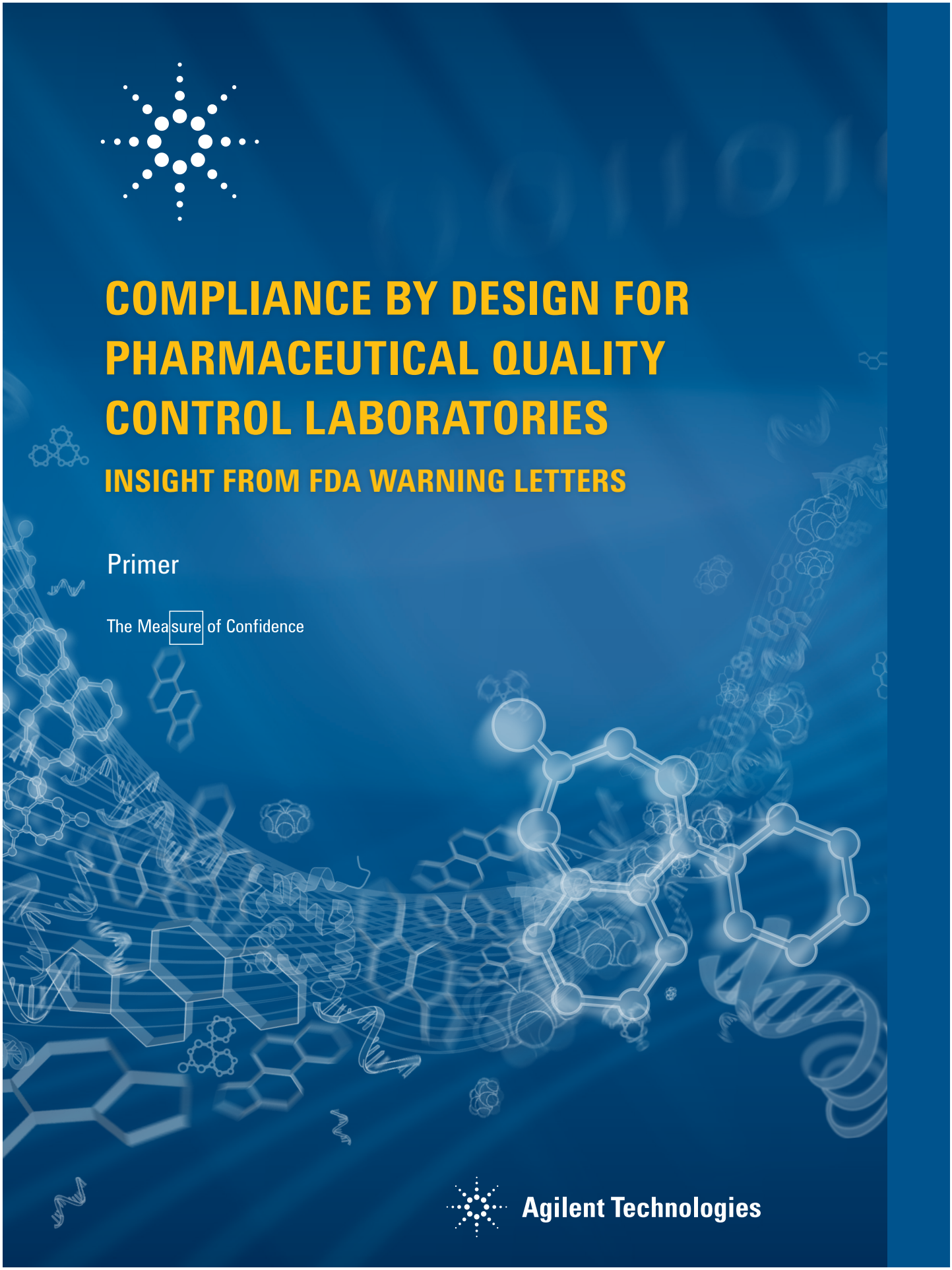

# COMPLIANCE BY DESIGN FOR PHARMACEUTICAL QUALITY CONTROL LABORATORIES

## INSIGHT FROM FDA WARNING LETTERS

Primer

The Measure of Confidence

Agilent Technologies

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# INTRODUCTION

The mission of the United States Food and Drug Administration (FDA) and equivalent international agencies is to protect consumer health and safety under the Federal Food, Drug, and Cosmetic Act or equivalent international laws. The agencies have developed two basic strategies towards this mission:

- Monitoring the quality of products through surveillance activities such as sampling and analyzing products in distribution.
- Evaluating through factory inspections the conditions under which products are developed, manufactured, tested, packed, labeled, and held.

Although the process and implementation of regulatory inspections are very similar for most regulatory agencies, they are best documented by the US FDA. This is one reason why this primer's focus is on US FDA inspections. Another reason is that more companies are affected by FDA inspections than by any other agency.

The FDA is expected to perform routine factory inspections every two years, and can also initiate "for cause" inspections for any reason, including poor quality of drugs found during routine monitoring of drugs on the market or as a result of other serious health risks that were brought to the FDA's attention.

Prior to product approval, the FDA conducts a pre-approval inspection; after the product has been approved, the FDA may conduct a post-approval inspection. In addition, when a firm makes a change to its product manufacturing process, the FDA should be notified. The FDA may choose to inspect the new process for compliance.

There has been a change from traditional inspections of profile classes towards risk-based system inspections. Safety for patients and consumers is the FDA's primary concern. As part of traditional inspections, FDA inspectors have checked compliance of a specific product during manufacturing stages across departments and systems, such as production areas, storage rooms, and laboratories. Since 2003, the FDA has been promoting the risk-based system inspections approach and has defined six systems:

1. Quality Systems: Assures overall compliance with cGMP and internal procedures. The quality assurance unit is part of this system in addition to Change Control, Management Controls, Corrective Action and Preventive Action (CAPA), and others.
2. Materials Systems: Includes measures and activities to control finished and in-process products, components, and closures. Validation of computerized inventory systems is a part of these systems.
3. Production Systems: Includes measures and activities to control the manufacture of drugs and drug products. Process validation and development of manufacturing procedures are part of these systems.
4. Laboratory Control Systems: Includes measures and activities related to laboratory procedures and processes from sampling to testing and archiving of laboratory records.
5. Packaging and Labeling Systems: Includes measures and activities that control the packaging and labeling of drugs. Validation of packaging and labeling operations is a part of these systems.
6. Facilities and Equipment: Includes the measures and activities that provide an appropriate physical environment and resources. Qualification of manufacturing equipment and cleaning validation is a part of these systems.

Quality systems are always inspected. The scope of this primer covers inspections of quality systems and laboratory control systems. During inspections, the FDA verifies that a firm's procedures and processes are in compliance with FDA GxP regulations such as Good Laboratory Practices, Good Clinical Practices, and Good Manufacturing Practices. If the FDA inspections identify deviations from the regulations, they will issue inspectional observations using 483 forms, also referred to as "483s" or inspectional observations. Depending on the severity of the deviations, instances of repeat observations, and a firm's response to the 483, the FDA may issue a formal letter listing some or all deviations of the 483, called an FDA Warning Letter.

While regulations and guidelines may typically endure unchanged for many years, interpretations, inspection, and enforcement practices undergo frequent changes and should be monitored regularly. Warning Letters, establishment inspection reports, and 483s (if publicly available) are ideal sources to find out what inspectors are looking for at specific times, and FDA press releases provide information on current FDA inspection policies.

In the last two years, an increasing number of firms have received FDA 483 inspection observations and Warning Letters. The FDA publishes most of the warning letters and some 483s and establishment reports on the Internet.[1,2] The European Medicines Agency (EMA) also has a website with information on inspection results,[3] making consumers, competitors, and business partners aware of a firm's non-compliance.

It is far beyond the scope of this primer to provide readers with detailed information on the necessary regulations and guidelines. The chapter of this primer entitled "Quality and Compliance in Quality Control Laboratories" provides an overview of the most important subjects. For more detailed information, further literature is available, including a 120-page primer on GLP and GMP.[4]

The chapter "Designing a QC Lab for Compliance: Reviewing Inspection Findings" will focus on frequently cited compliance deviations observed during FDA inspections. Several hundred GMP-related Warning Letters and inspection reports were analyzed. Readers can use this information to educate themselves on the current thinking of FDA inspectors as well as past mistakes made by other companies and how to avoid them. Based on information from these citations, certain best practices that can help design regulatory compliance into quality control laboratories have also been included.

## Resources for Additional Reading and More Complete Understanding

While this primer provides an overview of citations from FDA Warning Letters with advice on appropriate improvements with respect to observed deviations, there are a number of useful resources available from the FDA, other regulatory bodies, and private authors that help provide additional and more complete information including, but not limited to, the following:

- FDA Guide to Inspections of Pharmaceutical Quality Control Laboratories: This document is most relevant to the topic of this primer.[5]
- Drug Manufacturing Inspections Program.[6] Though not specific to laboratories, it offers useful information for QC labs.
- PIC/S Guide: Inspection of Pharmaceutical Quality Control Laboratories.[7] This guide has been developed for PIC/S inspectors in preparation for inspections of QC laboratories.
- FDA, Investigations Operations Manual, version 2014.[8] This document contains the most detailed information about FDA inspections. It is targeted to FDA inspectors, but also useful to read by regulated industry and other inspectors.
- FDA Warning Letter websites.[1,2,9]

# QUALITY AND COMPLIANCE IN QUALITY CONTROL LABORATORIES

Primary objectives of regulatory inspections are to (1) verify that the data measured in quality control laboratories are reliable and accurate, and (2) ensure that only safe and effective drugs are authorized for marketing and released for product shipment. QC laboratories are considered high-risk areas because they are often the final step verifying the quality of the drug prior to shipment. Therefore, they should follow GMP regulations to demonstrate the quality and integrity of data. Being in compliance is a prerequisite for successful FDA inspection. This chapter will give a brief overview of GMP requirements for pharmaceutical QC laboratories.

Compliance requirements for QC laboratories can be divided into two categories:

1. General quality system requirements that apply to all regulated activities within a firm, e.g., control of documents, internal audits, and qualification of personnel. These are called quality system requirements and typically are subject to the quality system inspection. Most of them are not specific to laboratories.
2. Laboratory-specific technical requirements that apply to specific situations in a laboratory, e.g., validation of analytical methods, verification of compendial methods, qualification of equipment, validation of computer systems, sampling, review, and approval of test reports.

## Compliance Overview

The overall impact of regulations on a pharmaceutical laboratory can be best illustrated by looking at the whole sample/data workflow (Figure 1). The upper part of the figure shows a typical laboratory workflow of samples and test data, together with key requirements underneath. The middle part shows GMP compliance requirements that are applicable to the entire sample or data workflow. The lower part shows general quality assurance requirements that are applicable not only to regulated laboratories but also to other departments within a firm.

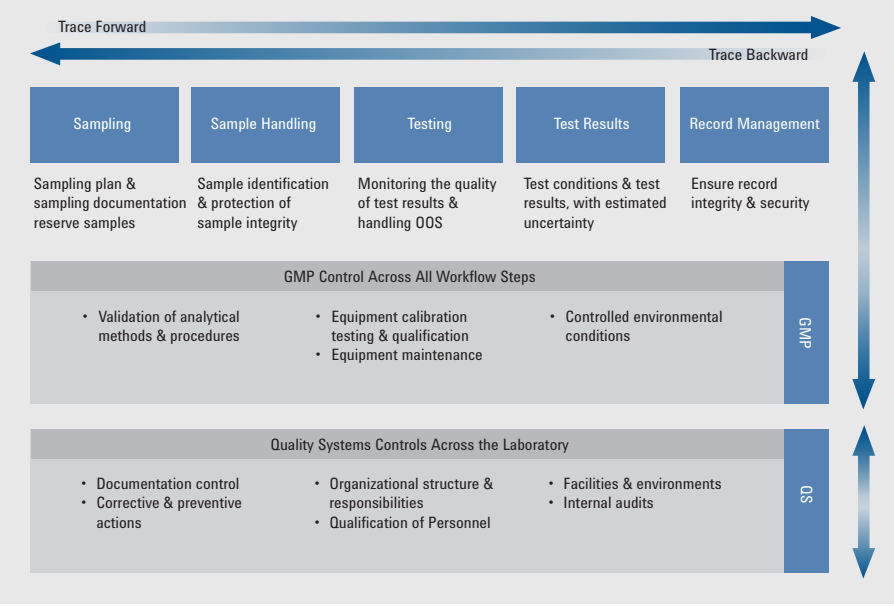


Figure 1: Quality Systems and Compliance along the Sample and Data Workflow

## Compliance for Individual Workflow Steps

All the individual workflow steps as shown in Figure 1 have specific requirements. These include:

- **Sampling**
  Sampling of substances, materials, or products for subsequent testing should follow a well-documented procedure. A sampling plan with a description of the sampling system, how sampling is performed, and by whom, should be in place. Sampling data should be recorded, such as sampling procedure used, location, the identification of the person who took the sample, and equipment used for sampling and environmental conditions, if relevant.
- **Sample Handling**
  Laboratories should ensure proper identification and protection of samples from the time the sample is taken until the time of its disposal. Receipt, protection, storage, processing, retention, and disposal should be described in a procedure. The procedure should include provisions for protection against deterioration, loss, or damage during transportation, handling, and storage.
- **Testing**
  Procedures for testing should ensure that only validated methods are used, that the equipment is qualified, and that sufficient system suitability test runs are conducted. Specifications and acceptance criteria should be defined for the sample to be tested. Procedures and parameters for testing should be documented. GMPs require that an investigation be conducted whenever a test result is observed that falls outside the previously specified acceptance criteria. This includes laboratory testing during the manufacture of APIs, raw material, and testing of finished products to the extent that cGMP regulations apply.
- **Test Results**
  Test results should be signed by the analyst and reviewed and approved by a second person, e.g., the analyst's supervisor or a member of the QA staff.
- **Record Management**
  All records associated with testing should be archived. Such records include certificates of analysis (COA), instrument and method parameters, supporting information such as chromatograms and spectra, and equipment qualification records. The archiving period is defined by individual regulations and can range from 6 to 15 years, and even beyond. Controls should be in place to ensure security, integrity, and availability of the records during the entire archiving period. Special attention should be paid to electronic records. They should have the ALCOA attributes; namely, Attributable (who generated them), Legible (are they readable), Contemporaneous (are they recorded in real-time), Original (are you sure they have not been changed), and are they Accurate?

## Compliance across All Workflow Steps

Some compliance requirements are applicable for all workflow steps. These are listed in the middle section of Figure 1, and include:

- **Validation of analytical methods and procedures**
  GMPs require analytical methods and procedures to be validated to demonstrate suitability for their intended use. The ultimate objective of the method validation process is to provide evidence that the method does what it is intended to do – accurately, reliably, and reproducibly. Typical method characteristics to be validated are: precision of amounts, reproducibility, specificity, linearity, accuracy, robustness, limit of quantitation, and limit of detection.
- **Equipment calibration and qualification**
  All equipment that impacts regulated activities should be qualified and computer systems should be validated. The objective is to provide evidence that the equipment and computer systems are suitable for intended use.
- **Equipment maintenance**
  Equipment should be well maintained to ensure proper ongoing performance. Procedures should be in place for regular preventive maintenance of hardware to detect and fix problems before they can have a negative impact on analytical data.
- **Controlled environmental conditions**
  Environmental conditions such as temperature and humidity should be controlled and monitored to ensure that they do not adversely affect the performance of equipment and material. Environmental requirements are typically provided by suppliers of equipment and material.

## Quality Assurance and Compliance across the Pharmaceutical Laboratory

Pharmaceutical laboratories are expected to follow quality assurance regulations. These include:

- **Documentation control**
  GMPs require that regulated documents be controlled from creation and approval through to distribution, archiving, and disposal. Typical documentation includes: policies, quality plans, master plans, standard operating procedures, and records such as analytical test records and training records.
- **Organizational structure and responsibilities**
  Organizational arrangements should be such that departments with conflicting interests do not adversely influence quality and compliance of data. For example, finance and the QA department should operate independently from laboratory activities. Tasks and responsibilities should be defined for each job.
- **Qualification of personnel**
  Personnel should be qualified for the assigned task. Qualification is based on education, experience in the job, and from training. The effectiveness of trainings should be verified and documented.
- **Facilities and environments**
  The laboratory should ensure that its facilities and environmental conditions do not adversely affect or invalidate sample handling, instrumentation, instrument calibration and qualification, and analytical testing.
- **Internal audits**
  Internal audits are a key element of any quality system. Their objective is to evaluate activities and existing documentation to confirm that these meet predetermined internal and/or external standards and/or regulations or customer requirements have been satisfied.

# DESIGNING A QC LAB FOR COMPLIANCE: REVIEWING INSPECTION FINDINGS

FDA Warning Letters can provide insight into the FDA's current and specific thinking on the interpretation of regulations, and offer valuable information for developing, improving, and implementing a compliance program. This chapter lists citations from Warning Letters categorized into various topics with best practices to enable lab managers and analysts to implement a compliance program. Areas where deviations have been observed:

- Quality system
- Documentation/procedures
- Vendor/supplier/service provider qualification
- Qualification of personnel
- Standard materials
- Validation of analytical procedures
- Laboratory equipment qualification
- Validation of laboratory computer systems
- Sampling and sample handling
- Testing and reporting of test results
- Handling out-of specification/out-of trend situations
- Data integrity and security

## Quality System

| Citation from Warning Letter | Best Practices |
|---|---|
| There is no robust quality system implemented. | Management and technical compliance deviations are generally associated with missing or inadequate quality systems. Corporate management is responsible for ensuring the quality and safety of drugs. Corporate management should initiate implementation of a global quality system using ICH Q10 "Pharmaceutical Quality Systems" as guidance. Laboratory operations managers are also advised to look at the management section of ISO/IEC 17025 as guidance. |
| Failure to establish management review procedures and failure to document the dates and results of these management reviews. | Management reviews are part of the quality system; they should be periodically conducted by top management to ensure continuous improvement of the quality system. The review should look at quality and other policies and critical procedures, management and supervisor reports, number and type of OOS results, corrective and preventive actions, internal and external audit results, inter-laboratory and proficiency testing, and customer feedback and complaints. |
| Failure of management with executive responsibility to ensure that the established quality policy is understood, implemented, and maintained at all levels of the organization. Management has not ensured that quality system requirements have been effectively established and maintained. | The corporate quality unit needs to initiate a firm-wide training program to make sure that all the concerned employees understand the quality system requirements. Successful implementation and ongoing maintenance of the quality system should be verified by local quality units, e.g., through random checks and regular audits. |
| Failure to establish procedures for implementing corrective and preventive action addressing the analysis of sources of quality data to identify existing and potential causes of non-conforming product or other quality problems. | Corrective and Preventive Actions (CAPA) are an important part of the quality system. An SOP should be developed on how to deal with identifying sources of quality problems, to correct problems and to anticipate potential problems that are currently not visible. Part of the procedure should describe how to verify the effectiveness of corrective and preventive actions. |

**Key points:**

- Corporate management is responsible for implementing robust global quality system.
- ICH Q10 and to some extent ISO/IEC 17025 can be used to establish a quality system in laboratory operations.
- A corporate-wide training and internal audit program should ensure that the quality system is understood, implemented at all levels, and maintained.

## Documentation/Procedures

| Citation from Warning Letter | Best Practices |
|---|---|
| During the inspection, our investigator requested to see investigations of out-of-specification (OOS) laboratory results and was informed that these investigations are conducted but not documented. | Documentation is important in all regulated areas. Any regulated activity that is not documented simply "didn't happen" for regulators. Therefore a procedure should be available that clearly describes all the regulated activities that need to be documented. |
| Failure to establish and maintain adequate procedures to control documents and ensure all obsolete documents are promptly removed from use or otherwise prevented from unintended use. | The procedure mentioned above should describe how official documents are initiated, authored, reviewed, approved, distributed, regularly reviewed, and updated. The procedure should also describe how people are trained on new and updated procedures and how obsolete documents are removed or otherwise indicated to be obsolete, e.g., through an expiration date. |
| No risk assessment performed to evaluate the effect of deviations from SOPs (standard operating procedures). | In case of any deviation from any SOP, the deviation should follow an SOP that describes circumstances of the deviation, including who needs to authorize a deviation, how the deviation should be documented, and a risk assessment on possible adverse events, with likelihood, severity, and risk mitigation steps. |
| Laboratory controls are deficient in that your firm has established procedures that allow for the averaging of out-of-specification (OOS) and within-specification analytical test results from separate sample runs. | Make sure that procedures (for laboratory controls) are correct according to current regulations and official guidelines. In this case, follow the FDA guide, "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production". |
| QC personnel failed to follow procedures in the conduct of GC calibrations. | There could be several reasons for this observation, including lack of training, lack of time, or the procedure being difficult to understand. In response to this warning letter, the firm should find out and document the correct reason and develop an adequate corrective and preventive plan. |
| Records are issued from the record storage room without any written checkout procedures. | Any document that is not used for day-to-day activities is transferred to the archive for the entire retention period. When the document is needed for temporary use, e.g., in preparation for FDA inspections or for scientific evaluations, checkout and return should follow an SOP. The procedure will describe access to the document, how checkout and return will be documented, and how the integrity of the returned document is ensured. |

**Key Points**

- Any regulated activity that is not documented simply "didn't happen" for regulators.
- Creation, distribution, and removal of documents from the archive should follow an SOP.
- Any regulated activity should follow written procedures. Procedures should be adequate for the task, training should be completed, procedures should be followed, and adherence to procedures should be confirmed.

## Vendor/Supplier/Service Provider Qualification

| Citation from Warning Letter | Best Practices |
|---|---|
| Failure to establish and maintain requirements that should be met by suppliers. For example, your firm has not specified quality requirements for suppliers, maintained lists of approved suppliers, and developed written procedures describing how suppliers are evaluated for quality acceptance requirements. | Include requirements for suppliers of equipment and material in the firm's compliance master plan. They should include clear criteria for the selection of suppliers. Most important is to define quality requirements for suppliers. Only suppliers meeting these requirements become approved suppliers. Be prepared to answer the question: why did you select a specific supplier? |
| There is no assurance that your firm establishes the reliability of the supplier's certificate of analysis (COA) through appropriate validation of the supplier's test results at appropriate intervals. The firm has no SOP for the qualification of the supplier, nor has such documented qualification been conducted. | Confirm that the material delivered by the supplier meets specification. In principle this can be done in two ways: (1) Test all incoming material and compare the results to the certificate of analysis (COA) supplied by the supplier. (2) As part of a quality agreement the supplier demonstrates in a supplier audit or otherwise how the material is tested to ensure compliance with specifications. Typically, quality is verified through a combination of 1 and 2. While initially the focus will be on testing, experience will show the reliability of the supplier's test results through consistent verification and documentation, potentially decreasing the frequency of testing of the incoming material. This process should follow an SOP. |
| Failure to evaluate potential suppliers and contractors. | Selection and qualification of suppliers should follow a procedure. The procedure should include a table with requirements and acceptance criteria. Examples for selection criteria include: history and size of the firm, previous experience with the supplier, recognition in the market place, and support. |
| The firm has been using the service provider for the testing of purified water; however there has been no audit conducted at this contract laboratory. | Develop a qualification program for service providers that is supported by a qualification agreement. Roles and responsibilities of both parties should be clearly defined. The agreement should mandate the service provider to fully describe the test procedures and how quality is ensured. |

## Vendor/Supplier/Service Provider Qualification

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm does not receive and review all raw data from contract testing laboratories. | Include in the quality agreement a statement, that the contract lab should submit all raw data from contract testing. Develop a procedure to review all received raw data in the same way as the sponsor firm. |
| The firm has no SOP for the qualification of vendors and contract laboratories, nor has such documented qualification been conducted. Calibration performed by an outside contractor not verified. | Develop and implement an SOP to qualify vendors and subcontractors. The SOP should state that subcontractor's activities should comply with GMP regulations. Critical work such as calibration and qualification and validation of computer systems should be verified to ensure that the activity complies with GMP standards. |

**Key Points**

- Quality agreements with suppliers of critical material and equipment, as well as for subcontractors, need to be in place.
- The agreement with the contract lab should ensure that the lab performs activities in line with your own regulatory and quality requirements.
- Selection of suppliers, service providers, and contract labs should follow a documented procedure and should be justified.
- There should be a process to ensure that incoming material conforms to previously written and agreed specifications.

## Qualification of Personnel

| Citation from Warning Letter | Best Practices |
|---|---|
| The formalized training program is inadequate in that it does not address current good manufacturing practices (cGMP). | The firm's training program should be documented in the compliance master plan or in a separate training master plan. The plan should specify what the personnel should be trained on. This includes training on not only the operational tasks but also on GMP. |
| Employees who manage, perform, and assess work that affects quality have not been adequately trained as members of the firm's quality unit. Quality assurance employees have not performed effectively in conducting complaint investigations, corrective/preventive action activities, design activities, internal audits, risk analysis, and/or document reviews. | Define department specific training requirements in the firm's training master plan. For example, managers and staff working in the quality unit should get trained on tasks that are specific to the quality unit, e.g., conducting complaint investigations, corrective/preventive action activities, design activities, internal audits, risk analysis, document reviews and approvals. |
| The firm's training program disclosed that there was no requirement for ongoing cGMP training of employees. The firm only had an initial cGMP training and did not provide regular cGMP training to all employees involved in the manufacture of drug products. There is no reference to cGMP training of supervisors or directors. | Training is not a one-time event, especially for items that can change over time, e.g., regulations, technology, and analytical methods. The type, frequency, and duration of re-training should be documented in the training master plan. For example, a refresher in GMP should occur annually. Duration should be a minimum of half a day. |

## Qualification of Personnel

| Citation from Warning Letter | Best Practices |
|---|---|
| There are no procedures defining training, qualification, disqualification, and re-qualification of sterility suite operators when they exceed the microbial limits defined. | Define person specific training requirements in a procedure that defines the person's tasks, qualification requirements, knowledge, resulting gaps, and training needs, and a plan for how to fill the gaps through training. The SOP should also define the type and frequency of update trainings. |
| The center director had not received any training on this computer system even though he retains a high security level for data entered on this computer system. | Trainings on using equipment and computer systems should be provided to whomever uses the system. This includes all management levels and all types of personnel, including staff with part-time jobs. |
| Supervisory employees have not documented any of their subordinates as being qualified to execute the analytical work to which they have been assigned. | Define in the training master plan that supervisors should document the assigned tasks of subordinates, qualification requirements, and how the qualification requirements are met, e.g., through education, job experience, or trainings. |
| The training program is limited to reading SOPs and does not require a demonstration of proficiency in job-specific procedures. | The training master plan should also state how training is documented and how the efficiency of the training is verified and documented. For example, successful training of an analyst can be demonstrated through successfully running a quality control sample using the same equipment and methodology as is used for the test samples the person will analyze. |

**Key Points**

- Develop a firm-wide training master plan that defines who should be trained on what, the type, duration, and frequency of training, and how the training is documented and the efficiency of training is verified.
- Develop a procedure (SOP) on how to document adequate qualification of employees. As the first step, the person's assigned tasks and qualification requirements should be documented. This should be compared with the person's knowledge gained through education or experience. Gaps between the requirements and knowledge should be filled with a training program.
- The quality unit should verify through internal audits the successful implementation of the training master plan and procedures.

## Standard Materials

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm has no system for the receipt and storage of standards and analytical chemicals. | Develop an SOP entitled "Standard Material" that describes how the quality of incoming material is ensured and how the quality and integrity of the material is maintained. For example, it should describe how the standards are stored, how they are protected from light during use in the laboratory, and how they are disposed of when no longer in use. |
| Expired standards were used in the calibration of equipment. There are no data to support extension of expiration for the standard. | Always make sure to use only standards that are not expired. In exceptional cases where the expiration date of standard material can be extended, stability or other required experiments should be performed to ensure the sustained quality of the standard. |
| No testing has been performed to certify any of your laboratory standards as secondary standards (e.g., testing against USP primary standards). The secondary reference standard in use has not been qualified. | Secondary or working standards can be used as long as quality has been compared with the primary or certified reference standard. The comparison should follow an SOP describing the test procedure, for example, it should state that validated methods should be used for the comparison. |
| Working solutions were not properly labeled or documented in laboratory notebooks. | For working or secondary standards, the same information should be available as for primary standard. In addition, they should include the name of the person who prepared the working standard, the location where it was prepared, and the procedure for how it was prepared. |

**Key Points**

- There should be an SOP on how to ensure the incoming quality of standard material and how to maintain the integrity and quality.
- When the expiration of standard material is extended, the ongoing quality of the standard should be verified through testing.
- Secondary standards can be prepared after adequate qualification using primary standards and labeling.

## Validation of Analytical Procedures

| Citation from Warning Letter | Best Practices |
|---|---|
| Accuracy, sensitivity, linearity, LOD, LOQ, and/or specificity were not assessed in the method validation. | Follow ICH Q2 "Validation of Analytical Procedures: Text and Methodology" for selecting the validation parameters for different analysis tasks, such as quantitative impurities, and for limit and identification tests. Be aware that the validation parameters listed in this and other FDA citations many times are not sufficient. ICH Q2 also has recommendations for test procedures.<br><br>Review the primer, "Validation of Analytical Methods"[10] for a comprehensive overview on all aspects of method validation. |
| Linearity and limits of detection were determined above the limit of the test. | Make sure that all the limits for actual testing such as linearity, limit of quantitation, limit of detection, and range are covered by the limits of the validation parameters. For example, if the sample concentration limit is 0.1%, the limit of quantitation should be determined at 0.05% or below. |
| All methods do not include system suitability tests to ensure that the system is operating properly. | System suitability testing is required by USP chapter <621>. The chapter lists minimum test parameters. Additional parameters are suggested for specific applications. For example, for quantitative impurity tests, the baseline noise of an HPLC detector should be routinely checked. The exact parameters and frequency of tests should be determined during method development when most detailed information is available on the methods robustness. The frequency of testing within a sample sequence run should be justified and documented in an SOP. |
| Failure to maintain complete records of any modification of an established method employed in testing. | Required records for method modification include: who has changed the method, why the method was changed, the date, and the old and new parameters. When computers are used to enter method parameters, information as listed above, plus the time, should be recorded by the computer in an electronic audit trail table. |

## Validation of Analytical Procedures

| Citation from Warning Letter | Best Practices |
|---|---|
| Alternate methods were used without demonstrating equivalence to current USP methods. | The US Food, Drug, and Cosmetic Act requires USP methodology be followed if available. The USP general notices have a statement that alternative methods can be used. The alternative method should be validated and the equivalency of the method to the USP methodology should be demonstrated through testing. For validation, best practices include following ICH Q2 and for equivalency testing best practices use comparative testing over the full linear range using well-characterized test samples. Be aware that when a firm uses alternative methods and has to submit samples to the FDA to verify submitted tests, the FDA will most likely follow USP methodology, and in case of any deviation between both tests the firm will have a hard time arguing that the USP method is the reason for the error. |
| Method verifications for compendial tests are not performed. | FDA 21 CFR Part 211 requires that any method, including compendial methods, should be verified to be suitable under actual conditions of use. USP general chapter <1226> should be used as a guideline for verification of compendial methods. |
| The test methods have not been verified to ensure suitability under actual conditions of use. Specifically, the firm failed to conduct adequate verification of USP compendial test methods as applied to the production of API. You assert that USP <1226>, Verification of Compendial Procedures, states that verification is not required for basic compendial test procedures that are routinely performed unless there is an indication that the compendial procedure is not appropriate for the article under test. We disagree with your assertions that verification is not required for those USP test methods used by your firm. | Not doing any testing to prove that the method is suitable for the intended use under actual conditions of use is not a good idea. Best practice is following USP <1226> and demonstrating the suitability of the method through system suitability testing supported by two validation experiments that are expected to be the most critical ones. |
| The firm uses USP methods to analyze products, but changes have been made to the USP methods and no validation has been performed. | USP allows for GC and HPLC through its chapter <621> changing parameters without revalidation for as long as the parameter changes are within the limits as specified by the chapter <621> and if the system passes system suitability testing. It may be appropriate to develop an SOP entitled "Change Versus Adjustments" of analytical methods according USP <621>". |

## Validation of Analytical Procedures

| Citation from Warning Letter | Best Practices |
|---|---|
| Methods that were validated at one facility and transferred to another site are being used without method transfer or revalidation protocol. | The process of method transfer with associated demonstration to prove that the method is suitable for its intended use in the receiving laboratory is documented in USP chapter <1224>. The chapter describes four options for the transfer: comparative testing, partial or full revalidation, co-validation, and doing nothing; however, doing nothing is never good advice in regulated environments. The most frequently applied option is comparative testing. A well-characterized sample is tested in the receiving lab and the method is formally transferred if the test results are within previously defined acceptance criteria. |
| Failure to follow the written stability testing program as required by 21 CFR 211.166(a), in that the firm has no validation data to demonstrate that the method used to analyze products for stability is capable of detecting degradation of the products. | Methods used for stability testing should be validated to be stability indicating. The validation parameters, tests, and acceptance criteria are to a large extent the same as for other analytical methods. The main objective is to ensure that the method can separate all degradants from each other and from the active drug substance. The biggest issue is to find samples that have the realistic types and concentrations of degradants. The sample should be made in the laboratory through forced degradation. The active substance is treated under elevated temperature, humidity, and light; the conditions are selected such that between 5 and 20% of the sample is degraded. The most important validation parameter is specificity, where spectrometric detectors (e.g., mass spectrometry) should be used in addition to standard HPLC equipment. |

**Key Points**

- All analytical methods used in regulated areas should be suitable for the intended use under actual conditions of use; in other words, they should be validated.
- The global standard for validation of analytical methods is the ICH Q2 Guide.
- The suitability of compendial methods follows USP chapter <1226> and the transfer of validated method between two different laboratories follows USP chapter <1224>.
- Changes to methods should be documented, and methods should be revalidated after the change. When computers are used to enter method parameters, the changes should be recorded in the electronic audit trail.
- When HPLC- and GC-based compendial methods are changed within the limits as defined in USP <621>, revalidation can be avoided if the method passes system suitability tests.
- Methods used for stability testing should be validated to be stability indicating. Test samples are generated through forced degradation.

## Laboratory Equipment Qualification

| Citation from Warning Letter | Best Practices |
|---|---|
| Failure of the quality control unit/laboratory to ensure that analytical instrumentation and test equipment used to assure the quality of the APIs has been appropriately qualified and calibrated for their intended use. | Start with a comprehensive equipment qualification master plan that should include a list of all laboratory equipment used in regulated environment. Use USP chapter <1058> as a framework for analytical equipment qualification. Allocate all equipment in one of the three USP categories A, B, and C. Define high-level qualification steps and documents to be developed for each category. Decide whether to qualify all or part of the equipment by your firm or through an external service provider.<br><br>Study the primer, "Analytical Instrument Qualification and System Validation"[11] to learn all about the approach and implementation of USP <1058>. |
| The calibration procedure for HPLC systems is inadequate in that it did not include the detector linearity, injector reproducibility, and the accuracy of temperature settings for the column heater. | Define detailed calibration and/or qualification procedures and acceptance criteria for each instrument category and develop SOPs for executing qualifications. |
| During the inspection, the firm did not provide an SOP for the performance verification of the HPLC and GC systems. Services for the verification of those systems are being contracted, and contractor's SOPs are being adopted. Each of them has different SOPs, which include different types of tests that do not compare. The firm should establish a procedure to assure uniformity, providing specific directions and requirements for all GC systems. Also, it will apply to HPLC systems. | Use the same harmonized procedure for the qualification of a specific instrument type that is independent of the manufacturer of the instrument and independent on who is providing the service. Otherwise discussions can come up why different procedures have been used for the same equipment. This can be facilitated by a service provider capable of qualifying instruments from different vendors. |
| Analytical balances are used outside specified range. | Define the operating range of each instrument as part of the requirement specification exercise. Ensure that the qualification range includes the specified operating range as required by the intended analytical procedures. |
| Failure to document equipment identification, calibration date, the individual performing the calibration, and the next calibration date. | Label the instruments with information on the last and next qualification dates, the person who performed the qualification, and the equipment asset number. Instruments that are not qualified should be labeled, "Not qualified, not for use". Alternatively, the equipment should be removed from the laboratory. |

## Laboratory Equipment Qualification

| Citation from Warning Letter | Best Practices |
|---|---|
| Your firm fails to maintain raw data associated with the requalification and calibration of your laboratory instruments. During the inspection, the investigators were informed that the annual re-qualification and calibration of your laboratory equipment (e.g., HPLC, GC, polarimeter, and analytical balance) is performed. However, you were unable to provide raw data or documentation regarding the qualification and calibration of your instruments and data to demonstrate that your quality unit reviewed and approved the work performed by your contractor. | During the review of the qualification work performed before approval, ensure that the qualification records are complete. Develop an SOP that defines what constitutes a complete record for each instrument. Examples are raw data, supporting material such as chromatograms and spectra, signatures of the engineer who performed the qualification, and the signature of a reviewer. When qualification is performed by a service provider, a representative of the user firm should verify and sign that the qualification was performed according to the user firm procedures. The qualification work (including tests, set points and limits) to be performed should be approved prior to the work being carried out. This review should address any differences between the qualification performed and the firm's procedures. This is a collaborative process. The qualification performed by a service provider may be scientifically equivalent, but different to that being previously performed. |
| Your firm has not cleaned and maintained equipment at appropriate intervals to prevent contamination that would alter the safety, identity, strength, or quality of the drug product. | Develop an SOP on "Maintenance of Equipment". The SOP should include steps, tasks, and a timetable for instrument cleaning and preventive maintenance activities. The SOP should also include or reference a table for documenting all cleaning and maintenance activities. |
| The balance used to weigh more than 20 mg did not comply with the USP 0.1% requirement for balance measurement uncertainty. | If USP methodology for equipment qualification and/or calibration is available, make sure that your procedure conforms to the current version of the chapter. The current mandatory chapter for balances is <41>. |
| Deviations pertaining to laboratory equipment failures were not investigated. During the review of the service report log books for HPLC and GC units, the investigator found many instances of servicing due to instrument problems that were not documented as deviations. | Any equipment malfunction that may have an impact on quality control testing should be appropriately recorded and investigated. Investigation should include an evaluation if the quality of test results, generated at or before the malfunction, could have been impacted. |
| There was no documentation that an investigation was conducted to determine the root cause of the failed calibrations of the gas chromatograph. In addition, your firm failed to implement adequate corrective action to prevent re-occurrence. | If calibration or qualification of equipment fails, the root cause for the failure should be identified. Once the root cause is identified, a corrective action should be initiated to correct the specific problem on that equipment. For example, if a wrong SOP was found to be the root cause, that SOP should be corrected, the equipment should be re-qualified, and after passing re-qualification criteria the updated SOP should be used for all other equipment of the same type. |

## Laboratory Equipment Qualification

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm did not perform re-qualification of the stability chambers. | Equipment qualification is not a one-time event; the FDA requires regular re-qualification. The tests and acceptance criteria should be the same as for the initial qualification. The frequency of re-qualification is instrument specific, and FDA officials frequently recommend asking equipment suppliers because they typically have the most experience. Best practice is to re-qualify chromatographic equipment yearly, unless a justified and documented risk assessment suggests shorter or longer cycles. |
| The HPLC performance qualification lacks sample energy (intensity of light source) and lamp use hours determination. | Performance qualification should ensure that the equipment runs on a day-to-day basis without any problem. Include measures into the system such as analysis of the function of critical parts (e.g., lamps) that directly impact the limits of detection and quantitation. Lamp usage time is one important factor, but ongoing measurement of the lamp energy is more meaningful.<br><br>For chromatography equipment, the relationship between work performed during a qualification and the tests included during routine use need to be clearly understood. For example, some aspects of instrument performance are evaluated each time the instrument is used, while others are evaluated during the qualification. |
| The laboratory does not verify that the calibration performed by an outside contractor is complete and performed as required by the established standard operating procedure "HPLC Maintenance and Operational Qualification". This SOP requires four tests for the operational verification: power up, diagnostics, accuracy, and reproducibility and linearity tests. The reproducibility and linearity tests have not been performed. | Before equipment qualification is outsourced to a service provider, the service provider should be approved by the firm to perform the work. Typically, this approval process includes a high level review of the quality system followed by the service provider to ensure that the procedures used have followed an appropriate development, validation and approval life cycle process in the their quality system. During the service provider approval process, any differences between the qualification work they will perform and the firm's requirements need to be addressed. In some cases, the firm's procedures may be updated, or where there is a regulatory requirement, the service provider may be able to configure the qualification work performed to meet the laboratory's requirements. Alternatively, any differences may be documented and justified. |

## Laboratory Equipment Qualification

| Citation from Warning Letter | Best Practices |
| --- | --- |
| The firm has failed to conduct adequate qualifications of the analytical instruments and test equipment. For example, the residual solvent method used to test the API has an initial starting gas chromatograph (GC) oven temperature of below 100˚C. Your firm's current qualification of the GC oven temperature does not include temperatures below 100˚C. | FDA often requires application specific equipment qualification set points. Best practice is that the qualification covers equipment settings that are also used for real sample analysis. Again, this requires flexibility on the part of the service provider in accommodating user-specific instrument set points. |

**Key Points**

- Develop an equipment qualification master plan listing all equipment to be qualified and describing the approach for equipment qualification.
- Use USP chapter <1058> as the framework for equipment qualification.
- Use scientific rational, and literature information to define test procedures for individual equipment.
- Use the same qualification procedure and acceptance criteria for the same type of equipment, regardless of the supplier.
- Label equipment with the qualification state. Ensure that only qualified equipment is used for sample analysis.
- Keep all raw data from qualification testing.
- Regularly conduct equipment cleaning and maintenance activities.
- If USP has a methodology for calibration or qualification, always use the current version.
- Investigate the root cause of failed calibration runs.
- When a QC lab outsources qualification activities, that QC lab is still responsible for the qualification.
- Develop and follow a schedule for regular re-qualification.

## Validation of Laboratory Computer Systems

| Citation from Warning Letter | Best Practices |
|---|---|
| Failure to adequately validate computer software for its intended use. | Validation of software and computer systems should adopt a life cycle approach to comply with regulatory requirements. Start with a validation plan followed by specifications requirement, risk assessment, vendor assessment, installation and verification testing; develop and implement procedures such as change control, revalidation and review to maintain the system in a validated state. Study chapter four and related references of the Agilent primer, "Analytical Instrument Qualification and System Validation" for more details.[11] Also see FDA's General Principles of Software Validation; Final Guidance for Industry and FDA Staff, 2002 |
| High-load situations of the computer have not been tested to prove that the system can run several applications in parallel at the same time, as documented in the user requirement specifications. | Laboratory computer systems should not only be tested under routine/easy conditions but also under high-load conditions according to the user requirement specifications (URS). For example, if the URS specifies that a computerized mass spectrometry system can run in parallel with a document management system, a test should include running both systems at the same time. Or, if the URS specifies a computerized HPLC system can control up to four HPLCs, one test should include a scenario with four HPLCs controlled by the computer system. |
| Training database software validation used to document employee training was deficient, in that the test scripts were not available to show the execution of the software validation protocol. It appears that at least five (5) tests specified in the approved protocol were not performed. | As part of operational qualification, a test plan should be developed that includes the test objective, acceptance criteria, and steps for testing, with expected documentation of test results. Before testing, the test plan should be approved by quality assurance and a senior validation engineer. After execution, the test protocols should be signed by the test engineer and QA should verify and confirm through signing that the test protocols have been executed according to the test plan. |
| Complete diagrams and text descriptions identifying all other network program interfaces have not been maintained or updated from original design specifications. | For complex systems such as networked client-server laboratory data systems, easy-to-understand system diagrams should be created that can be used to explain sample and data flow. These diagrams are regulated documents, and should be version controlled and updated whenever the system is changed. |

## Validation of Laboratory Computer Systems

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm relied on the computer system validation only performed at the vendor site; no testing was performed at the user's site. | As part of the validation plan, develop a test plan that demonstrates, based on risk assessment, that the system reliably works at the user's site. At a minimum, all functions that have been configured at the user's site should be tested, e.g., limited and authorized access to the system, electronic audit trail, and network configuration settings. In addition, perform a system test that executes all critical functions. For a chromatographic data system, these include instrument control, data acquisition, peak integration, and other data processing steps, as well as reporting, archiving, and data retrieval. |
| No person from the firm reviewed or approved the third-party test results. | When a QC lab outsources validation of software and computer systems to a third party, the QC lab is still responsible for the validation. Therefore, best practice is for the QC lab to review and approve the validation report. |
| Failure to have an adequate validation procedure for computerized spreadsheets used for in-process and finished product analytical calculations. | Develop an SOP regarding validation and use of spreadsheet applications. The procedure should verify that the results generated by the spreadsheet are correct, that the formulas used for any calculation are documented, and that the spreadsheet is put under rigorous change control. The SOP should also ensure that users only use spreadsheet templates that are designed by the laboratory and that the exact spreadsheet used is documented as part of the result output. |
| There is no SOP for determining the degree of testing necessary to assure the proper function of the system following any hardware or software modifications. | Develop an SOP for change control of software and computer systems. The procedure should describe how to initiate, authorize, implement, validate, and document any changes. |

## Validation of Laboratory Computer Systems

| Citation from Warning Letter | Best Practices |
|---|---|
| There are no SOPs in place for periodically revalidating and challenging the software program to assure data acquired on the system is accurate and reliable for the determination of the purity and potency of products. | Even though software by itself may not change over time, the surrounding hardware peripherals and network interfaces change frequently. Therefore, ongoing correct functioning of the software in the selected environment should be demonstrated either through a full operational re-qualification and/or through a regular review of the system. |
| No IQ, OQ, or PQ has been performed throughout the life of the system. No validation reports have been generated historically. | Non-validated software and computer systems should not be used in an FDA regulated environment. In such cases, stop using the system immediately and retrospectively validate the system following the same principles as for a new system. Part of the exercise should be an evaluation of the system's impact on test results generated by the non-validated system. |

**Key Points**

- Software and computer systems used in an FDA regulated environment should be validated (21 CFR Part 11 Section 11.10a).
- Validation of software and computer systems should follow a life cycle approach to comply with regulatory requirements.
- As part of the validation plan, develop a test plan with acceptance criteria and all required steps for testing. Prepare diagrams for complex systems such as client-server networked laboratory data systems.
- Software developed and tested at the vendor's site still requires functional testing at the user's site.
- Excel spreadsheet applications should be validated.
- Changes to computer hardware and software should be controlled.
- Software and computer systems require periodic review and/or revalidation.

## Sampling and Sample Handling

| Citation from Warning Letter | Best Practices |
|---|---|
| Failure to establish and maintain procedures to ensure that sampling methods are adequate for their intended use, and that sampling plans are written based on a valid statistical rationale. | Develop a sampling plan that includes the method of sampling, the number of units per batch to be tested based on statistical rationale, the equipment to be used, the amount of sample to be taken, documentation of how representative sampling is ensured, instructions for any required subdivision of the sample, the type and condition of the sample container to be used, and Instructions for cleaning and storing the sampling tools. |

## Sampling and Sample Handling

| Citation from Warning Letter | Best Practices |
|---|---|
| Representative samples are not taken of each shipment of each lot of components and drug product containers for testing or examination. | Develop an SOP to collect representative samples of each shipment for product testing. The number of containers to be sampled and the amount of material to be taken from each container should be based on appropriate criteria, such as statistical criteria for component variability, confidence levels, the degree of precision desired, and the quantity needed for analysis plus the quantity needed for the reserve sample. |
| Certain elements of sample integrity are addressed in SOPs, but none of the procedures explicitly call for maintaining sample integrity throughout the testing of the sample. | Develop a procedure to ensure the integrity of the sample throughout its entire use. This includes procedures for the transportation, receipt, handling, protection, storage, retention, and/or disposal of test items. |
| The reserve sample of drug product does not consist of at least twice the quantity necessary to perform all the required tests of drug product. | Best practice is that the reserve sample consist of 2.5 times the quantity necessary to perform all required tests. |
| Reserve samples from representative sample lots or batches of drug products are not examined visually at least once a year for evidence of deterioration. | FDA GMP 21 CFR 211, like other GMP regulations, requires reserve samples to be examined visually at least once a year for evidence of deterioration, such as precipitation of solid material, color changes or volume loss due to evaporation of volatile liquids. Investigate any evidence of deterioration and document the results of the examination and any investigation with other stability data on the drug product. |
| Drug product reserve samples are not stored in the same immediate container-closure system or one that has essentially the same characteristics as used for the marketed product. | Retain the reserve sample for at least one year beyond the expiration date of the corresponding product batch. The sample should be retained under the exact same conditions as the marketed products, either in the same container-closure system used to store the marketed drug product or one that has essentially the same characteristics. |

**Key Points**

- Sampling should follow a sampling plan.
- The sampling plan should ensure that samples are representative.
- Ensure integrity of the sample through the entire use.
- Take 2.5 times the sample size for reserve samples.
- Store the reserve sample under the same conditions as the marketed product.
- Visually inspect the reserve sample every year.

## Testing and Reporting of Test Results

| Citation from Warning Letter | Best Practices |
|---|---|
| Failure to perform laboratory testing on each batch of drug product prior to release in order to determine satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient. | Include a high-level statement in the compliance master plan that each batch of a product should be tested to determine the product's conformance to specifications. Develop a procedure for performing such testing, to include setting acceptance criteria, verification by the analysts that the used equipment is qualified, and verification that the test method is validated. |
| A QC operator interviewed during the inspection stated that integrations are performed and re-performed until the chromatographic peaks are "good", but was unable to provide an explanation for the manner in which integration is performed. | Develop an SOP on how to manually integrate and re-integrate chromatographic peaks. The procedure should include examples of when re-integration is and is not allowed, and whether re-integration has to be approved. Each re-integration step should be recorded, along with the reason for the re-integration, the re-integration method, and the re-integration results. The steps should be recorded by the electronic audit trail. |
| The chromatography raw data does not include the processing method used to produce the final analytical results. Laboratory records did not always include a description and identification of the sample received for testing, the date the sample was taken, the date the sample was received for testing, and the data derived from testing. | Ensure that all information as required by GMPs is available and includes chromatographic processing methods, as well as calculations used to convert raw data to final results and information on sampling and the test sample. Study FDA 21 CFR 211.194, which lists required laboratory records, and developing an SOP accordingly. The SOP should include or refer to a checklist used by the reviewer of the test results.<br><br>The FDA expects that all entries in logbooks, batch records, laboratory documentation, and all other documentation be signed by the person who performed the operation. Having a supervisor signature does not give the same level of accountability.<br><br>Ensure that each critical record is signed by the person who generated the record. For example, an analytical test result should be signed by the analyst who performed the test. |

## Testing and Reporting of Test Results

| Citation from Warning Letter | Best Practices |
|---|---|
| There were not always the initials or signature of a second person showing that the original records have been adequately reviewed by a second person. | Critical records should be reviewed by a second person. For example, after the analyst signs analytical test results, a reviewer should also review and sign off on these results. The FDA does not specify the job function of the reviewer but typically recommends that the reviewer be independent; therefore, someone from QA is considered to be more independent than a lab supervisor. The tasks of the reviewer should be defined in an SOP. If the tasks are technical in nature, for example, judging adequate chromatographic peak integration based on integration marks, the reviewer should be a QA person with a laboratory background. |

**Key Points**

- Each batch of a product should be tested to determine the product's conformance to specifications.
- Manual integration and re-integration should follow documented procedures.
- Check FDA 21 CFR 211.194 for records that should be available for each sample analysis.
- Test results should be signed by the analyst.
- Test results should be signed by a reviewer, ideally a QA person with QC lab experience.

## Handling Out-of-Specification/ Out-of-Trend Situations

| Citation from Warning Letter | Best Practices |
|---|---|
| The chromatographic test data reflecting the out-of-specification test results were not recorded in laboratory notebooks. Instead, a new sample preparation was injected within the same chromatographic run without supervisory approval. | Any OOS result obtained should be investigated and documented according to an SOP. This procedure should include analysis of the data, assessment of the extent and cause of the problem, allocation of the tasks for corrective actions, and conclusions. Study the FDA guide, "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" in preparation for drafting the procedure. |
| The investigation was not extended to other batches that may have been associated with the specific failure or deviation. | Conduct three steps for a successful OOS investigation: (1) Identify the root cause of the error, (2) Correct the error, and (3) Extend the OOS to other batches to investigate if the problem could also occur at other batches; if so, the corrective action should also be implemented for all batches that could have been affected. |

## Handling Out-of-Specification/ Out-of-Trend Situations

| Citation from Warning Letter | Best Practices |
|---|---|
| Extraneous HPLC peaks were continuously explained to be auto injector contamination, with no further investigation. | Investigate atypical results such as extraneous HPLC peaks until the root case is identified and the problem is corrected and successful correction verified. |
| Your firm lacked a trend analysis of your sample results. | Develop an SOP for handling out of trend (OOT) results. Run about 5% of your sample runs as quality control samples and generate quality control charts with alert and OOT limits. Quality control samples generating results above the alert limits are OOT results and should be investigated. |
| Although results above your alert limits may be an indication of an ongoing uncorrected problem, no investigation was conducted to identify a potential root cause of the problem. | If alert limits are generated during trend analysis, an investigation should be initiated to avoid OOS results arising from failure to investigate and correct the root case of the alert. |
| The inspection revealed that batch samples were retested until acceptable results were obtained. | Develop an SOP for handling OOS results. Follow the FDA Guide, "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production" in preparation for drafting the procedure. The guide states that a failure investigation should be initiated after an OOS situation and testing should be stopped. |

**Key Points**

- Any OOS result should be investigated according to the FDA Guide, "Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production".
- Extend the investigation to similar batches.
- Investigate all atypical results such as extraneous HPLC peaks.
- Perform trend analysis with corrective actions to avoid OOS situations.

## Data Integrity and Security

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm routinely designated method validation chemists, lead chemists, and laboratory supervisors, as system administrators with the ability to modify and delete raw data files in the HPLC data acquisition system. | Develop administrator and technical controls to prevent analysts and supervisors from having the ability to modify and delete raw data files and other critical records. Develop, implement, and enforce administrator and technical controls to prevent analysts and supervisors from having the ability to modify and delete raw data files and other critical records. |
| The audit trail function for the chromatographic systems was disabled at the time of the inspection. | Use software with an audit trail function that cannot be switched off, or one that can only be switched off by system administrators. |
| The firm needed to upgrade several pieces of their equipment. Principally, the old HPLC being used still was using the equivalent of a strip chart recorder. | Select, purchase, install, and validate a chromatographic data system with functionality to enable users to comply with 21 CFR Part 11. |

## Data Integrity and Security

| Citation from Warning Letter | Best Practices |
|---|---|
| The firm's response did not include an audit of past chromatographic data to determine whether data used to support release and stability studies originated from appropriately integrated chromatograms. | Any data integrity–related corrective action should always include an assessment of whether and to what extent the integrity issue could have impacted past data. |
| The firm failed to prevent deterioration or deletion of the back-up data. | Physically secure your data back-up system or otherwise limit access to the data, e.g., through electronic security. |
| The audit trail does not truly reflect the identity of the responsible individuals. Individuals have been able to log on to the system under another individual's account and make changes that then show up on the audit trail to the first individual. | Develop procedural and technical controls to get access to the system and data through unique individual user specific user and password control. Train all users on the new process. Verify that the electronic audit trail function records changes made by specific users are reported under that specific user's name. As a preventive action, implement the same process and software functionality on all regulated systems in the lab. |
| The firm's review of laboratory data does not include the audit trail/revision history to determine if unapproved changes have been made. | Create a list of approved and unapproved changes. QA informs all users of the system that unapproved changes are strictly forbidden, that all changes will be recorded by the electronic audit trail, and that QA will review electronic audit trail records. Include in the QA data review checklist an item stating, "Review audit trail for unapproved changes". |
| The computers in the lab do not time-out. If an employee fails to log off a computer and walks away, other individuals can easily access the computer under the first employee's account. | Develop and implement an SOP for automated system time-out after a period of certain user-system inactivity. Justify and document the specified inactivity time based on risk assessment. For high-risk systems, the inactivity time should be shorter. Criteria for risk assessment include how critically the system records are for patient safety, and the number of people who could access the system. |
| Data security protocols are not established for describing the user's roles and responsibilities in terms of their privileges to access, change, modify, create, and delete projects and data. | Develop a procedure to define and implement user privileges to access the system and create or delete data. The lab manager together with Quality Assurance should define the privileges based on the individual's role and responsibility. |
| There is no procedure to back up data from the personal computer (PC) connected to the HPLC and the UV/Vis spectrophotometer. | Develop a general procedure to regularly back up regulated data. The IT department should set up a validated automated back-up program and train users on its use, including how to retrieve data lost on the working PC. As a preventive action, implement the same procedure on all other regulated systems. |

## Data Integrity and Security

| Citation from Warning Letter | Best Practices |
|---|---|
| Validation of the laboratory software used to control instruments, generate data, perform calculations, and store data from raw material and finished product testing failed to demonstrate adequate security. | Develop a validation procedure with test protocols to verify correct functioning of all security features. For example, procedures related to restricted access (i.e. allowing only authorized individual users) to systems and data should be verified. |
| The worksheet dated September 18, 2013 reports "sample wt. taken wrongly." However, the correction to the stability data sheet for this lot gives the appearance that sample weighing was performed on August 10, 2013. | Develop and enforce an SOP for documentation practices to ensure that analysts always record data in a contemporaneous manner, by prohibiting back-dating data or re-creating results without supporting documents. Train all analysts and supervisors accordingly. |
| The firm did not retain complete raw data from testing performed to ensure the quality of your APIs. Specifically, your firm deleted all electronic raw data supporting your high performance liquid chromatography (HPLC) testing of all API products released to the U.S. market. | Define original electronic files as raw data for HPLC analysis and for similar and more complex techniques. Develop procedural and technical controls to ensure that electronic raw data files are saved, together with the audit trail table and with application software to enable review of raw data during inspections. Train analysts accordingly. As a preventive action, implement this procedure in all regulated HPLC and similar systems. |

**Key Points**

- Develop administrative and technical controls preventing people working in the QC lab from deleting raw data.
- Make sure that the electronic audit trail function is implemented, validated, and always switched on.
- Have an independent reviewer review the electronic audit trail table.
- Back up data daily. Validate the back-up and retrieval procedure.
- Implement an automated program for display inactivity time-out.
- Implement privileges for system access and the creation, modification, or deletion of data.
- Verify correct functioning of all security features.
- Ensure that analysts always record data in a contemporaneous manner.
- Define and retain original electronic files as raw data for HPLC analyses.

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Printed in the USA January 15, 2015
5991-5456EN

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