GUIDE TO INSPECTIONS OF PHARMACEUTICAL QUALITY CONTROL LABORATORIES

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1. INTRODUCTION

The pharmaceutical quality control laboratory serves one of the most important functions in pharmaceutical production and control. A significant portion of the CGMP regulations (21 CFR 211) pertain to the quality control laboratory and product testing. Similar concepts apply to bulk drugs.

This inspection guide supplements other inspectional information contained in other agency inspectional guidance documents. For example, Compliance Program 7346.832 requiring pre-approval NDA/ANDA inspections contains general instructions to conduct product specific NDA/ANDA inspection audits to measure compliance with the applications and CGMP requirements. This includes pharmaceutical laboratories used for in-process and finished product testing.

2. OBJECTIVE

The specific objective will be spelled out prior to the inspection. The laboratory inspection may be limited to specific issues, or the inspection may encompass a comprehensive evaluation of the laboratory's compliance with CGMP's. As a minimum, each pharmaceutical quality control laboratory should receive a comprehensive GMP evaluation each two years as part of the statutory inspection obligation.

In general these inspections may include

-- the specific methodology which will be used to test a new product

-- a complete assessment of laboratory's conformance with GMP's

-- a specific aspect of laboratory operations

3. INSPECTION PREPARATION

FDA Inspection Guides are based on the team inspection approach and our inspection of a laboratory is consistent with this concept. As part of our effort to achieve uniformity and consistency in laboratory inspections, we expect that complex, highly technical and specialized testing equipment, procedures and data manipulations, as well as scientific laboratory operations will be evaluated by an experienced laboratory analyst with specialized knowledge in such matters.

District management makes the final decision regarding the assignment of personnel to inspections. Nevertheless, we expect investigators, analysts and others to work as teams and to advise management when additional expertise is required to complete a meaningful inspection.

Team members participating in a pre-approval inspection must read and be familiar with Compliance

Program 7346.832, Pre-Approval Inspections/Investigations. Relevant sections of the NDA or ANDA should be reviewed prior to the inspection; but if the application is not available from any other source, this review will have to be conducted using the company's copy of the application.

Team members should meet, if possible, prior to the inspection to discuss the approach to the inspection, to define the roles of the team members, and to establish goals for completion of the assignment. Responsibilities for development of all reports should also be established prior to the inspection. This includes the preparation of the FDA 483.

The Center for Drug Evaluation and Research (CDER) may have issued deficiency letters listing problems that the sponsor must correct prior to the approval of NDA/ANDA's and supplements. The inspection team is expected to review such letters on file at the district office, and they are expected to ask the plant for access to such letters. The team should evaluate the replies to these letters to assure that the data are accurate and authentic. Complete the inspection even though there has been no response to these letters or when the response is judged inadequate.

4. INSPECTION APPROACH

A. General

In addition to the general approach utilized in a drug CGMP inspection, the inspection of a laboratory requires the use of observations of the laboratory in operation and of the raw laboratory data to evaluate compliance with CGMP's and to specifically carry out the commitments in an application or DMF. When conducting a comprehensive inspection of a laboratory, all aspects of the laboratory operations will be evaluated.

Laboratory records and logs represent a vital source of information that allows a complete overview of the technical ability of the staff and of overall quality control procedures. SOPs should be complete and adequate and the operations of the laboratories should conform to the written procedures. Specifications and analytical procedures should be suitable and, as applicable, in conformance with application commitments and compendial requirements.

Evaluate raw laboratory data, laboratory procedures and methods, laboratory equipment,including maintenance and calibration, and methods validation data to determine the overall quality of the laboratory operation and the ability to comply with CGMP regulations.

Examine chromatograms and spectra for evidence of impurities, poor technique, or lack of instrument calibration.

Most manufacturers use systems that provide for the investigation of laboratory test failures. These are generally recorded in some type of log. Ask to see results of analyses for lots of product that have failed to meet specifications and review the analysis of lots that have been retested, rejected, or reworked. Evaluate the decision to release lots of product when the laboratory results indicate that the lot failed to meet specifications and determine who released them.

B. Pre-Approval

Documents relating to the formulation of the product, synthesis of the bulk drug substance, product specifications, analysis of the product, and others are examined during the review process in headquarters. However, these reviews and evaluations depend on accurate and authentic data that truly represents the product.

Pre-approval inspections are designed to determine if the data submitted in an application are

authentic and accurate and if the procedures listed in the application were actually used to produce the data contained in the application. Additionally, they are designed to confirm that plants (including the quality control laboratory) are in compliance with CGMP regulations.

The analytical sections of drug applications usually contain only test results and the methods used to obtain them. Sponsors are not required to file all the test data because such action would require voluminous submissions and would often result in filing redundant information. Sponsors may deliberately or unintentionally select and report data showing that a drug is safe and effective and deserves to be approved. The inspection team must decide if there is valid and scientific justification for the failure to report data which demonstrates the product failed to meet its predetermined specifications.

Coordination between headquarters and the field is essential for a complete review of the application and the plant. Experienced investigators and analysts may contact the review chemist (with appropriate supervisory concurrence) when questions concerning specifications and standards arise.

Inspections should compare the results of analyses submitted with results of analysis of other batches that may have been produced. Evaluate the methods and note any exceptions to the procedures or equipment actually used from those listed in the application and confirm that it is the same method listed in the application. The analyst is expected to evaluate raw laboratory data for tests performed on the test batches (biobatches and clinical batches) and to compare this raw data to the data filed in the application.

5. FAILURE (OUT-OF-

SPECIFICATION) LABORATORY

RESULTS

Evaluate the company's system to investigate laboratory test failures. These investigations represent a key issue in deciding whether a product may be released or rejected and form the basis for retesting, and resampling.

In a recent court decision the judge used the term "out-of-specification" (OOS) laboratory result rather than the term "product failure" which is more common to FDA investigators and analysts. He ruled that an OOS result identified as a laboratory error by a failure investigation or an outlier test. The court provided explicit limitations on the use of outlier tests and these are discussed in a later segment of this document., or overcome by retesting. The court ruled on the use of retesting which is covered in a later segment of this document. is not a product failure. OOS results fall into three categories:

-- laboratory error

-- non-process related or operator error

-- process related or manufacturing process error

A. LABORATORY ERRORS

Laboratory errors occur when analysts make mistakes in following the method of analysis, use incorrect standards, and/or simply miscalculate the data. Laboratory errors must be determined through a failure investigation to identify the cause of the OOS. Once the nature of the OOS result has been identified it can be classified into one of the three categories above. The inquiry may vary

with the object under investigation.

B. LABORATORY INVESTIGATIONS

The exact cause of analyst error or mistake can be difficult to determine specifically and it is unrealistic to expect that analyst error will always be determined and documented. Nevertheless, a laboratory investigation consists of more than a retest. The inability to identify an error's cause with confidence affects retesting procedures, not the investigation inquiry required for the initial OOS result.

The firm's analyst should follow a written procedure, checking off each step as it is completed during the analytical procedure. We expect laboratory test data to be recorded directly in notebooks; use of scrap paper and loose paper must be avoided. These common sense measures enhance the accuracy and integrity of data.

Review and evaluate the laboratory SOP for product failure investigations. Specific procedures must be followed when single and multiple OOS results are investigated. For the single OOS result the investigation should include the following steps and these inquiries must be conducted before there is a retest of the sample:

o the analyst conducting the test should report the OOS result to the supervisor

o the analyst and the supervisor should conduct an informal laboratory investigation which addresses the following areas:

1. discuss the testing procedure

2. discuss the calculation

3. examine the instruments

4. review the notebooks containing the OOS result

An alternative means to invalidate an initial OOS result, provided the failure investigation proves inconclusive, is the "outlier" test. However, specific restrictions must be placed on the use of this test.

1. Firms cannot frequently reject results on this basis.

2. The USP standards govern its use in specific cases only.

3. The test cannot be used for chemical testing results. An initial content uniformity test was OOS followed by a passing retest. The initial OOS result was claimed the result of analyst error based on a statistical evaluation of the data. The court ruled that the use of an outlier test is inappropriate in this case..

4. It is never appropriate to utilize outlier tests for a statistically based test, i.e., content uniformity and dissolution.

Determine if the firm uses an outlier test and evaluate the SOP.

Determine that a full scale inquiry has been made for multiple OOS results. This inquiry involves quality control and quality assurance personnel in addition to laboratory workers to identify exact process or non process related errors.

When the laboratory investigation is inconclusive (reason for the error is not identified) the firm:

1. Cannot conduct 2 retests and base release on average of three tests

2. Cannot use outlier test in chemical tests

3. Cannot use a re-sample to assume a sampling or preparation error

4. Can conduct a retest of different tablets from the same sample when a retest is considered appropriate (see criteria elsewhere)

C. FORMAL INVESTIGATIONS

Formal investigations extending beyond the laboratory must follow an outline with particular attention to corrective action. The company must:

1. State the reason for the investigation

2. Provide summation of the process sequences that may have caused the problem

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

4. List other batches and products possibly affected, the results of investigation of these batches and products, and any corrective action. Specifically:

o examine other batches of product made by the errant employee or machine

o examine other products produced by the errant process or operation

5. Preserve the comments and signatures of all production and quality control personnel who conducted the investigation and approved any reprocessed material after additional testing

D. INVESTIGATION DOCUMENTATION

Analyst's mistakes, such as undetected calculation errors, should be specified with particularity and supported by evidence. Investigations along with conclusions reached must be preserved with written documentation that enumerates each step of the investigation. The evaluation, conclusion and corrective action, if any, should be preserved in an investigation or failure report and placed into a central file.

E. INVESTIGATION TIME FRAMES

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.

6. PRODUCT FAILURES

An OOS laboratory result can be overcome (invalidated) when laboratory error has been documented. However, non-process and process related errors resulting from operators making mistakes, equipment (other than laboratory equipment) malfunctions, or a manufacturing process that is fundamentally deficient, such as an improper mixing time, represent product failures.

Examine the results of investigations using the guidance in section 5 above and evaluate the decision to release, retest, or rework products.

7. RETESTING

Evaluate the company's retesting SOP for compliance with scientifically sound and appropriate procedures. A very important ruling in one recent court decision sets forth a procedure to govern the retesting program. This district court ruling provides an excellent guide to use in evaluating some aspects of a pharmaceutical laboratory, but should not be considered as law, regulation or binding legal precedent. The court ruled that a firm should have a predetermined testing procedure and it should consider a point at which testing ends and the product is evaluated. If results are not satisfactory, the product is rejected.

Additionally, the company should consider all retest results in the context of the overall record of the product. This includes the history of the product. The court ordered a recall of one batch of product on the basis of an initial content uniformity failure and no basis to invalidate the test result and on a history of content uniformity problems with the product., type of test performed, and in-process test results. Failing assay results cannot be disregarded simply on the basis of acceptable content uniformity results.

The number of retests performed before a firm concludes that an unexplained OOS result is invalid or that a product is unacceptable is a matter of scientific judgment. The goal of retesting is to isolate OOS results but retesting cannot continue ad infinitum.

In the case of nonprocess and process-related errors, retesting is suspect. Because the initial tests are genuine, in these circumstances, additional testing alone cannot contribute to product quality. The court acknowledged that some retesting may precede a finding of nonprocess or process-based errors. Once this determination is made, however, additional retesting for purposes of testing a product into compliance is not acceptable.

For example, in the case of content uniformity testing designed to detect variability in the blend or tablets, failing and non-failing results are not inherently inconsistent and passing results on limited retesting do not rule out the possibility that the batch is not uniform. As part of the investigation firms should consider the record of previous batches, since similar or related failures on different batches would be a cause of concern.

Retesting following an OOS result is ruled appropriate only after the failure investigation is underway and the failure investigation determines in part whether retesting is appropriate. It is appropriate when analyst error is documented or the review of analyst's work is "inconclusive" , but it is not appropriate for known and undisputed non-process or process related errors.

The court ruled that retesting:

o must be done on the same, not a different sample

o may be done on a second aliquot from the same portion of the sample that was the source of the first aliquot

o may be done on a portion of the same larger sample previously collected for laboratory purposes

8. RESAMPLING

Firms cannot rely on resampling. The court ordered the recall of one batch of product after having

concluded that a successful resample result alone cannot invalidate an initial OOS result. to release a product that has failed testing and retesting unless the failure investigation discloses evidence that the original sample is not representative or was improperly prepared.

Evaluate each resampling activity for compliance with this guidance.

9. AVERAGING RESULTS OF

ANALYSIS

Averaging can be a rational and valid approach when the object under consideration is total product assay, but as a general rule this practice should be avoided. The court ruled that the firm must recall a batch that was released for content uniformity on the basis of averaged test results. because averages hide the variability among individual test results. This phenomenon is particularly troubling if testing generates both OOS and passing individual results which when averaged are within specification. Here, relying on the average figure without examining and explaining the individual OOS results is highly misleading and unacceptable.

Content uniformity and dissolution results never should be averaged to obtain a passing value.

In the case of microbiological turbidimetric and plate assays an average is preferred by the USP. In this case, it is good practice to include OOS results in the average unless an outlier test (microbiological assays) suggests the OOS is an anomaly.

10. BLEND SAMPLING AND

TESTING

The laboratory serves a vital function in blend testing which is necessary to increase the likelihood of detecting inferior batches. Blend uniformity testing cannot be waived in favor of total reliance on finished product testing because finished product testing is limited.

One court has ruled that sample size influences ultimate blend test results and that the sample size should resemble the dosage size. Any other practice would blur differences in portions of the blend and defeat the object of the test. If a sample larger than the unit must be taken initially, aliquots which resemble the dosage size should be carefully removed for the test, retests, and reserve samples. Obviously, the initial larger sample should not be subjected to any additional mixing or manipulation prior to removing test aliquots as this may obscure non-homogeneity.

Multiple individual blend uniformity samples taken from different areas cannot be composited. However when variation testing is not the object of assay testing, compositing is permitted.

If firms sample product from sites other than the blender, they must demonstrate through validation that their sampling technique is representative of all portions and concentrations of the blend. This means that the samples must be representative of those sites that might be problems; e.g. weak or hot spots in the blend.

11. MICROBIOLOGICAL

The review of microbiological data on applicable dosage forms is best performed by the microbiologist (analyst). Data that should be reviewed include preservative effectiveness testing, bioburden data, and product specific microbiological testing and methods.

Review bioburden (before filtration and/or sterilization) from both an endotoxin and sterility perspective. For drug substance labs evaluate methods validation and raw data for sterility, endotoxin testing, environmental monitoring, and filter and filtration validation. Also, evaluate the methods used to test and establish bioburdens.

Refer to the Microbiological Inspection Guide for additional information concerning the inspection of microbiological laboratories.

12. SAMPLING

Samples will be collected on pre-approval inspections. Follow the sampling guidelines in CP 7346.832, Part III, pages 5 and 6.

13. LABORATORY RECORDS AND

DOCUMENTATION

Review personal analytical notebooks kept by the analysts in the laboratory and compare them with the worksheets and general lab notebooks and records. Be prepared to examine all records and worksheets for accuracy and authenticity and to verify that raw data are retained to support the conclusions found in laboratory results.

Review laboratory logs for the sequence of analysis versus the sequence of manufacturing dates. Test dates should correspond to the dates when the sample should have been in the laboratory. If there is a computer data base, determine the protocols for making changes to the data. There should be an audit trail for changes to data.

We expect raw laboratory data to be maintained in bound, (not loose or scrap sheets of paper), books or on analytical sheets for which there is accountability, such as prenumbered sheets. For most of those manufacturers which had duplicate sets of records or "raw data", non-numbered loose sheets of paper were employed. Some companies use discs or tapes as raw data and for the storage of data. Such systems have also been accepted provided they have been defined (with raw data identified) and validated.

Carefully examine and evaluate laboratory logs, worksheets and other records containing the raw data such as weighings, dilutions, the condition of instruments, and calculations. Note whether raw data are missing, if records have been rewritten, or if correction fluid has been used to conceal errors. Results should not be changed without explanation. Cross reference the data that has been corrected to authenticate it. Products cannot be "tested into compliance" by arbitrarily labeling out-of-specification lab results as "laboratory errors" without an investigation resulting in scientifically valid criteria.

Test results should not have been transcribed without retention of the original records, nor should test results be recorded selectively. For example, investigations have uncovered the use of loose sheets of paper with subsequent selective transcriptions of good data to analyst worksheets and/or workbooks. Absorbance values and calculations have even been found on desk calendars.

Cut charts with injections missing, deletion of files in direct data entry systems, indirect data entry without verification, and changes to computerized programs to override program features should be carefully examined. These practices raise questions about the overall quality of data.

The firm should have a written explanation when injections, particularly from a series are missing from the official work-sheets or from files and are included among the raw data. Multiple injections

recorded should be in consecutive files with consecutive injection times recorded. Expect to see written justification for the deletion of all files.

Determine the adequacy of the firm's procedures to ensure that all valid laboratory data are considered by the firm in their determination of acceptability of components, in-process, finished product, and retained stability samples. Laboratory logs and documents when cross referenced may show that data has been discarded by company officials who decided to release the product without a satisfactory explanation of the results showing the product fails to meet the specifications. Evaluate the justification for disregarding test results that show the product failed to meet specifications.

14. LABORATORY STANDARD

SOLUTIONS

Ascertain that suitable standards are being used (i.e. in-date, stored properly). Check for the reuse of stock solutions without assuring their stability. Stock solutions are frequently stored in the laboratory refrigerator. Examine the laboratory refrigerators for these solutions and when found check for appropriate identification. Review records of standard solution preparation to assure complete and accurate documentation. It is highly unlikely that a firm can "accurately and consistently weigh" to the same microgram. Therefore data showing this level of standardization or pattern is suspect and should be carefully investigated.

15. METHODS VALIDATION

Information regarding the validation of methods should be carefully evaluated for completeness, accuracy and reliability. In particular, if a compendial method exists, but the firm chooses to use an alternate method instead, they must compare the two and demonstrate that the in-house method is equivalent or superior to the official procedure. For compendial methods firms must demonstrate that the method works under the actual conditions of use.

Methods can be validated in a number of ways. Methods appearing in the USP are considered validated and they are considered validated if part of an approved ANDA. Also a company can conduct a validation study on their method. System suitability data alone is insufficient for and does not constitute method validation.

In the review of method validation data, it is expected that data for repetitive testing be consistent and that the varying concentrations of test solutions provide linear results. Many assay and impurity tests are now HPLC, and it is expected that the precision of these assays be equal or less than the RSD's for system suitability testing. The analytical performance parameters listed in the USP XXII, <1225>, under the heading of Validation of Compendial Methods, can be used as a guide for determining the analytical parameters (e.g., accuracy, precision, linearity, ruggedness, etc.) needed to validate the method.

16. EQUIPMENT

Laboratory equipment usage, maintenance, calibration logs, repair records, and maintenance SOPs also should be examined. The existence of the equipment specified in the analytical methods should be confirmed and its condition noted. Verify that the equipment was present and in good working order at the time the batches were analyzed. Determine whether equipment is being used properly.

In addition, verify that the equipment in any application was in good working order when it was listed as used to produce clinical or biobatches. One would have to suspect the data that are generated from a piece of equipment that is known to be defective. Therefore, continuing to use and release product

on the basis of such equipment represents a serious violation of CGMP's.

17. RAW MATERIAL TESTING

Some inspections include the coverage of the manufacturer of the drug substance. The safety and efficacy of the finished dosage form is largely dependent on the purity and quality of the bulk active drug substance. Examine the raw data reflecting the analysis of the drug substance including purity tests, charts, etc.

Check the impurity profiles of the BPC used in the biobatch and clinical production batches to determine if it is the same as that being used to manufacture full scale production batches. Determine if the manufacturer has a program to audit the certificate of analysis of the BPC, and, if so, check the results of these tests. Report findings where there is substantial difference in impurity profiles and other test results.

Some older compendial methods may not be capable of detecting impurities as necessary to enable the control of the manufacturing process, and newer methods have been developed to test these products. Such methods must be validated to ensure that they are adequate for analytical purposes in the control and validation of the BPC manufacturing process. The drug substance manufacturer must have complete knowledge of the manufacturing process and the potential impurities that may appear in the drug substance. These impurities cannot be evaluated without a suitable method and one that has been validated.

Physical tests such as particle size for raw materials, adhesion tests for patches, and extrusion tests for syringes are essential tests to assure consistent operation of the production and control system and to assure quality and efficacy. Some of these tests are filed in applications and others may be established by the protocols used to manufacture the product. The validation of methods for such tests are as important as the test for chemical attributes.

Physical properties tests often require the use of unique equipment and protocols. These tests may not be reproducible in other laboratories, therefore, on site evaluation is essential.

18. IN PROCESS CONTROLS AND

SPECIFICATIONS

Evaluate the test results from in-process tests performed in the production areas or laboratory for conformance with established sampling and testing protocols, analytical methods, and specifications. For example, evaluate the tests for weight variation, hardness, and friability. These tests may be performed every fifteen or thirty minutes during tableting or encapsulating procedures. All testing must comply with CGMP's.

The drug application may contain some of the in-process testing plan, including methods and specifications. The inspection must confirm that the in-process tests were done, as described in the plan, and ascertain that the results were within specifications. The laboratory work for the lengthier tests should also be reviewed.

The methods used for in-process testing may differ from those used for release testings. Usually, whether the methods are the same or different, the specifications may be tighter for the in-process tests. A product with a 90.0%-110.0% assay release specification may have a limit of 95.%-105.0% for the in-process blend. Some of the tests done may differ from those done at release. For example, a firm may perform disintegration testing as an in-process test but dissolution testing as a release test.

Expect to see consistent in-process test results within batches and between batches of the same formulation/process (including development or exhibit batches). If this is not the case, expect to see scientific data to justify the variation.

19. STABILITY

A stability-indicating method must be used to test the samples of the batch. If there is no stability-indicating assay additional assay procedures such as TLC should be used to supplement the general assay method. Evidence that the method is stability indicating must be presented, even for compendial methods.

Manufacturers may be required to accelerate or force degradation of a product to demonstrate that the test is stability indicating. In some cases the sponsor of ANDA's may be able to search the literature and find background data for the specificity of a particular method. This information may also be obtained from the supplier of the drug substance. Validation would then be relatively straightforward, with the typical parameters listed in the USP in chapter <1225> on validation of compendial methods addressed as applicable.

Evaluate the manufacturer's validation report for their stability testing. Again, review the raw laboratory data and the results of testing at the various stations to determine if the data actually reported matches the data found in on site records.

Evaluate the raw data used to generate the data filed documenting that the method is stability indicating and the level of impurities.

20. COMPUTERIZED LABORATORY

DATA ACQUISITION SYSTEMS

The use of computerized laboratory data acquisition systems is not new and is addressed in the following CGMP guidance documents:

o Compliance Policy Guide 7132a.07 Computerized Drug Processing: Input/Output Checking.

o Compliance Policy Guide 7132a.08 Computerized Drug Processing: Identification of "Persons" on Batch Production and Control Records.

o Compliance Policy Guide 7132a.11 Computerized Drug Processing: CGMP Applicability to Hardware and Software

o Compliance Policy Guide 7132a.12 Computerized Drug Processing: Vendor Responsibility

o Compliance Policy Guide 7132a.15 Computerized Drug Processing: Source Code for Process Control Application Programs

o Guide to Inspection of Computerized Systems in Drug Processing.

It is important, for computerized and non computerized systems, to define the universe of data that will be collected, the procedures to collect it, and the means to verify its accuracy. Equally important are the procedure to audit data and programs and the process for correcting errors. Several issues must be addressed when evaluating computerized laboratory systems. These include data collection, processing, data integrity, and security.

Procedures should only be judged adequate when data are secure, raw data are not accidentally lost, and data cannot be tampered with. The system must assure that raw data are stored and actually processed.

The agency has provided some basic guidance on security and authenticity issues for computerized systems:

o Provision must be made so that only authorized individuals can make data entries.

o Data entries may not be deleted. Changes must be made in the form of amendments.

o The data base must be made as tamperproof as possible.

o The Standard Operating Procedures must describe the procedures for ensuring the validity of the data.

One basic aspect of validation of laboratory computerized data acquisition requires a comparison of data from the specific instrument with that same data electronically transmitted through the system and emanating on a printer. Periodic data comparisons would be sufficient only when such comparisons have been made over a sufficient period of time to assure that the computerized system produces consistent and valid results.

21. LABORATORY MANAGEMENT

Overall management of the laboratory work, its staff, and the evaluation of the results of analysis are important elements in the evaluation of a control laboratory. Span of supervisory control, personnel qualifications, turnover of analysts, and scope of the laboratory's responsibility are important issues to examine when determining the quality of overall management and supervision of work. Individually or collectively, these factors are the basis for an objection only when they are shown to result in inadequate performance of responsibilities required by the CGMPs.

Review laboratory logs for the sequence of analysis and the sequence of manufacturing dates. Examine laboratory records and logs for vital information about the technical competence of the staff and the quality control procedures used in the laboratory.

Observe analysts performing the operations described in the application. There is no substitute for actually seeing the work performed and noting whether good technique is used. You should not stand over the analysts, but watch from a distance and evaluate their actions.

Sometimes the company's employees have insufficient training or time to recognize situations that require further investigation and explanation. Instead they accept unexplained peaks in chromatograms with no effort to identify them. They may accept stability test results showing an apparent increase in the assay of the drug with the passage of time with no apparent question about the result. Also, diminishing reproducibility in HPLC chromatograms appearing several hours after system suitability is established is accepted without question.

Good manufacturing practice regulations require an active training program and the documented evaluation of the training of analysts.

The authority to delete files and override computer systems should be thoroughly examined. Evaluate the history of changes to programs used for calculations. Certain changes may require management to re-examine the data for products already released.

ENDNOTES