Goals

When you have completed this unit, you should be able to:

- Understand what the GMP requirements are for the analytical quality laboratory and stability testing laboratory
- Identify which GMP regulations govern the analytical quality laboratory
- Use a range of information tools, from the contents of this training in support of analytical testing and stability testing auditing.
- Recognize compliance or non-compliance of analytical quality laboratory and stability testing

Definitions

Acceptance Criteria: The criteria a product must meet to successfully achieve delivery requirements.

Analyte: A substance being analyzed, a single component (compound) of a mixture

Chromatography: The science which studies the separation of molecules based on differences in their structure and/or composition. Chromatography is also a method to separate components of an analyte involving a mobile phase moving through a stationary phase. Types of chromatography are thin layer chromatography, gas chromatography, liquid chromatography and paper chromatography.

Chromatogram: The record of results for the process of chromatography that shows the response of each component as a function of time and concentration of the sample. The record may be the media itself, e.g. the paper or thin layer medium, a piece of paper (e.g. computer print out) or it may be retained in a computer and displayed on video display terminal.

Consistency: The ability of the instrument to test the same sample numerous times under the same conditions and generate the same data within in a very strict range.

Detection limit: The detection limit of an individual analytical procedure is the lowest amount of analyte in a sample which can be detected but not necessarily quantitated as an exact value. This is considered to be 3 times the signal to noise ratio, within PAR&D.

Gas chromatography (GC): A type of chromatography where a liquid sample is vaporized and then injected into a column on a carrier gas. Components of the analyte bind to the column at different rates, with different parts of the analyte passing through the column at different times.

High performance liquid chromatography (HPLC): A type of chromatography using relatively high pressures and small diameter column packings to achieve sharp and highly reproducible elution profiles.

Laboratory Information Management System (LIMS): A system which can be used to schedule and record analytical data.

about some of the tests that can be performed in a laboratory to increase the auditor's understanding of the analytical laboratory environment.

Topics included in this section of the training unit are:

- Importance of laboratory audits
- Laboratory administration, organization and personnel training
- General condition of laboratory
- Sample receipt and tracking
- Analytical testing concepts and methods validation
- Reference standards/reagents/volumetric solutions
- Documentation-procedures, SOPs, records and reports
- Instrumentation and equipment-
- OOS investigations
- Quality standards
- Change control program
- Stability testing
- Reserve/Retained sample testing
- Certificate of Analysis

The Importance of the Laboratory Audit

An audit of the quality analytical laboratory is important for a number of reasons. Testing is performed to assure that the drug product meets acceptance criteria throughout the drug manufacturing process and its shelf life. Shown below are the types of testing the analytical laboratory performs and the benefits of the testing.

Type of Testing	Benefit
Raw Material or components	Prevent unacceptable components from being used.
In-process testing	Identify potential problems before the product moves to the next manufacturing stage. Product may be able to be re-worked/reprocessed, salvaging the batch.
Active substance testing **Final/release testing**	Confirm the purity and quality. Allow final product to be distributed to the market or for clinical trials with the knowledge that the product is safe, pure, and effective.
Stability testing	Confirm that development products or products in the market maintain identity, strength, potency, purity and quality.
Cleaning validation	Detect residual chemical.

Because testing is so important, analytical laboratory techniques and instrumentation must perform within their specified limits continually. Documentation must be accurate and complete.

To assure this, there must be laboratory controls in place, including:

- Specifications, test methods and sampling plans in place that are approved.
- Deviations and changes must be documented and justified
- Tests must be conducted to determine conformance to specifications

Linearity is another analytical parameter. A sample should be able to be diluted and assayed with the assay results directly proportional to the concentration of the analyte in the sample. If the test has good linearity, the plot of the results should yield a straight line

The specificity of a method defines the ability of the method to measure the analyte of interest to the exclusion of other relevant components. The test should be specific enough that even if there are other components in the sample, only one component is measured.

Each method will have a range. The range of the method is the area between the lower and the upper limits of quantitation. The range should be linear.

The detection limit, also known as the Limit of Detection, allows the laboratory analyst to determine if a particular analyte is present but may not provide a quantity of the analyte. If an analytical instrument is used, it is usually the smallest concentration of analyte the instrument is able to "see".

Quantification limit, also known as the Limit of Quantification, is the smallest amount (lowest concentration) that an analyte can be measured accurately and precisely. The detection limit and the quantification limit may be different for the same instrument being used.

Ruggedness refers to the degree of reproducibility of test results obtained by the analysis of the same samples under a variety of normal test conditions. Some examples of these include testing in different laboratories, using different analysts, conducting the tests on different instruments, using different lots of reagents, using different elapsed times, performing assays on different days. Ruggedness is normally expressed as the lack of influence of operational and environmental variables of the analytical method on test results.

Robustness is the capacity to remain unaffected by small, but deliberate variations in the method parameters and provide an indication of its reliability.

Most analytical laboratory test methods are validated using some of these parameters.

Test method validation

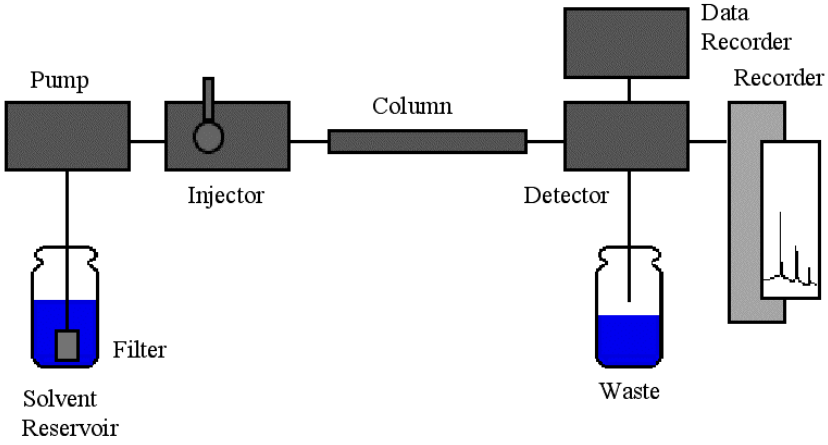
All analytical procedures, which are used to generate data that could be included in a regulatory submission, must be validated to the degree appropriate for the phase of development before use. Full validation should be preformed during phase III of the development. Analytical procedures that are used to test a commercial finished product, active ingredient, raw material or packaging component, must be validated before use.

Records should be in place to show what was done during the validation testing. Methods can be validated in a number of ways. If a site uses a method that appears in the USP (or other official compendia) it is considered validated, but the method must be shown to work under the actual conditions that it will be used (method qualification). A method is also considered validated if it is part of an approved NDA. A site can also conduct a validation study on their method. However, system suitability data alone is not sufficient to validate a method.

Method validation data must be consistent and conform to acceptance criteria. Validation results from a number of different tests, conducted under the same conditions, must demonstrate repeatability. When using varying concentrations of test solutions, the results must be linear. Many assay and impurity tests now use HPLC. It is expected that the

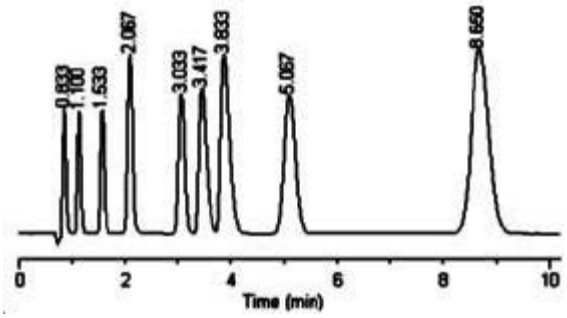
Methods

High Pressure Liquid Chromatography (HPLC)



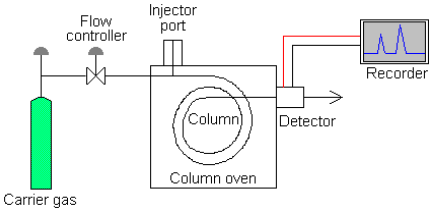
HPLC works by pumping the mobile phase, composed of a solvent, through a column (the stationary phase) under very high pressure. The analyte is injected into the moving phase or solvent, and carried through the column. In HPLC, all analytes travel the same distance (the length of the column), so compounds are characterized by retention time (i.e. the time that an analyte remains in the column). Once the analyte is eluted, it passes through a detector where data is integrated. This data is then transformed into a chromatogram.

HPLC Instrument



HPLC Chromatogram

Gas chromatography



Gas chromatography is also a separation method for mixtures of chemicals. The carrier gas acts as the moving phase. The sample, usually a liquid, is injected into the gas, and then carried through the column. A detector is attached to the end of the column.

Certificate of Analysis

A Certificate of Analysis should be produced where appropriate to detail the testing completed on a batch. There should be processes in place to ensure the accuracy of the certificate.

Summary

Since the analytical quality laboratory provides information that is used for release of our drug product, it is important that the laboratory follows GMP. The goal of the laboratory should be that the correct samples have the required testing performed. To accomplish this,

- Analytical methods must be validated and appropriately used to test the samples
- Laboratory personnel must be trained
- Equipment and instrumentation must be qualified, calibrated and maintained
- Documentation must be complete and accurate.
- Appropriate systems must be in place to manage OOS and OOT results, investigations, routine preventative maintenance, and change control

Key Parameters in Auditing Analytical Quality Laboratories

Prior to the audit

- Find out which products are tested and the test methods used
- Choose at least one product with specifications and test methods as detailed in the Marketing Authorization/NDA/CTA/IND/JNDA to follow during the audit.
- Request a list of laboratory SOPs
- Review relevant Quality agreement.
- Request a list of laboratory equipment
- Request a list of laboratory deviations/OOS/OOT investigations from the previous 12 months
- Review previous audits and regulatory audits to determine if there are pending actions

During the audit

- Conduct a walk through of the laboratory by following the path of a sample to be tested. Include sample storage areas and chambers.
  - Receiving and tracking samples
    - Ensure samples are labeled properly and uniquely identified.
    - Ensure that there is a system in place that assures samples are stored under correct conditions.
    - If samples are subdivided for multiple tests, ensure that the subdivision is recorded.
    - If samples are pooled for analysis, ensure that the pooling is recorded.
    - Ensure that the sample is signed in using a well documented and established procedure.
    - Ensure that there is a documented procedure for logging samples out of the laboratory.
    - Ensure that site requirements for sample handling and storage are included in a laboratory SOP.
    - Ensure that samples are managed and stored based on their storage and handling instructions.
    - Check how the laboratory handles ‘non routine samples’ e.g. for experimental work. How these are controlled, logged into the laboratory and results recorded.