

**Auditing an Analytical Quality & Stability Testing Laboratory**

<b>Title: Auditing an Analytical Quality &amp; Stability Testing Laboratory</b>					
<b>Auditor Manual: 015</b>					
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**Audit Training Manual: 015**

**Auditing an Analytical Quality &  
Stability Testing Laboratory**

## Auditing an Analytical Quality & Stability Testing Laboratory

**Linearity:** The linearity of an analytical procedure is its ability (within a given range) to obtain test results which are directly proportional to the concentration (amount) of analyte in the sample. For those analytical procedures which are not linear, another mathematical relationship (proportionality) must be demonstrated.

**Method Validation:** The process by which it is established, by laboratory studies, that the performance characteristics of the analytical methods meet the requirements for the intended application.

**New Drug Application (NDA):** Application to the US regulatory agency (FDA) to allow the sponsor to market a drug product in the US.

**Marketing Authorisation Application (MAA):** Application for authorisation to place medicinal products on market. This is a specific term for the EU/EAA markets.

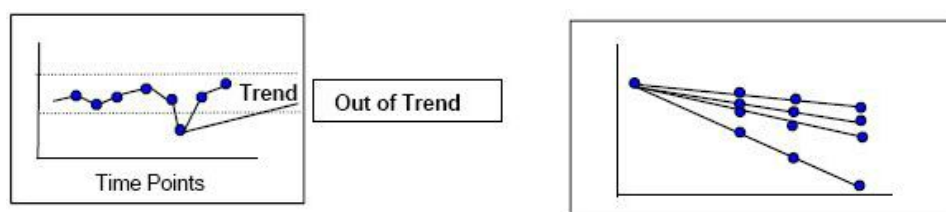
**Japanese New Drug Application (JNDA):** Application to be submitted for regulatory drug approval to the Japanese Ministry of Health, Labour and Welfare (MHLW).

**Clinical Trial Application (CTA):** An application to regulatory authority(ies) for the permission to perform a clinical study using an investigational product in subject/patients. Defined in ICH guideline for GCP, May 1996.

**Investigation New Drug Application (IND):** A new drug that is used in a clinical investigation application.

**Out-of-specification (OOS) result:** A laboratory test that is outside its regulatory or compendial limits. In some cases, there may be additional tests and/or limits that are used to assess the quality of a material, but are not included in registrations or compendia. In these cases, the general principles described here are useful, but more latitude is allowable in the disposition of the material as long as it meets its legal requirements.

**Out-of-trend (OOT) result:** A laboratory test that is within its regulatory or compendial limit but is atypical of previous results for the test over a number of batches or earlier time points in a stability study and may provide early indication of a potential OOS result. The importance of OOT results increases as the knowledge of the product increases and more latitude in interpretation of, and response to, an OOT result may be appropriate in early development compared to commercial product.



**Precision:** The precision of an analytical procedure expresses the closeness of agreement (degree of scatter) between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision should be measured using authentic samples. However, if it is not possible to obtain a homogeneous sample it may be measured using artificially prepared samples or a sample solution. The precision of an analytical procedure is usually expressed as the variance, standard deviation or coefficient of variation of a series of measurements.

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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.

<b>Type of Testing</b>	<b>Benefit</b>
<b>Raw Material or components</b>	Prevent unacceptable components from being used.
<b>In-process testing</b>	Identify potential problems before the product moves to the next manufacturing stage. Product may be able to be re-worked/reprocessed, salvaging the batch.
<b>Active substance testing</b> <b>Final/release testing</b>	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.
<b>Stability testing</b>	Confirm that development products or products in the market maintain identity, strength, potency, purity and quality.
<b>Cleaning validation</b>	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

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### Sample Receipt and Tracking

The laboratory should have a procedure and system in place to manage samples. When receiving samples, the laboratory should record the name or identification of the sample as indicated in the site's SOP, type of sample, date received, type of storage needed (i.e. refrigeration, protected from light, etc.), and signature of person who received it. The sample may be entered into a validated computer system (e.g. LIMS) or manually into a logbook if it is controlled. The laboratory should account for all samples coming into the laboratory (i.e. each sample that is received in the laboratory should undergo testing). Once the sample has been received it needs to be tested within an established time frame.

### Analytical Testing Concepts and Methods Validation

Analytical testing is performed to:

- Identify what components are in the drug product, raw materials and active substance.
- Determine if the correct components are present
- Determine if the components are present in the correct concentration/amount
- Determine the quality of the product whose chemical constitution is critical
- Determine if there are any chemicals present that should not be

To do this, the test methods must meet certain analytical parameters. The basic validation parameters for test methods are:

- Precision
- Accuracy
- Specificity
- Detection limit
- Quantification limit
- Linearity
- Range
- System suitability
- Robustness
- Ruggedness

Precision is reproducibility, repeatability or consistency. An example is an arrow hitting a target. The number of arrows that hit the same area or near the same area give a value for precision.



Good Precision



Poor Precision

Accuracy is getting results that are within the specifications. In the case of an arrow hitting the target, the goal is to have all the arrows hit the center of the target.



Good Precision  
Poor Accuracy



Poor Precision  
Poor Accuracy



Good Precision  
Good Accuracy

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precision of these assays be equal or less than the RSD's for system suitability testing. Analytical performance parameters listed in the USP/NF (current version), <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.

To perform the test, reference standards, reagents and volumetric solutions are needed as part of the assay. They must be prepared correctly and meet their specifications.

### Reference Standards, Volumetric Solutions and Reagents

Procedures for working with reference standards, volumetric solutions, and reagents used in the analytical quality laboratory should be approved and in place. These procedures should include:

- Which reference standards are used first if there is more than one lot of standard
- How to qualify the standard, whether through in house testing or Certificate of Analysis from the manufacturer
- When and how reference standards and volumetric solutions should be recertified, and the documentation requirements for recertification
- How the reference standards and volumetric solutions should be stored and monitored
- How reference standards should be used (i.e. “as is” or “dry before use”)

Reagents should have their expiration date clearly marked on the container. Storage instructions and lot number should not be obscured if a label is attached by the laboratory. If a reagent is used in a preparation its lot number should be recorded.

### Documentation

It is expected that all procedures, records and reports accurately represent both the actual in-use testing process and accurate data. Documents that should be reviewed, as applicable, during a laboratory audit should include information about the laboratory itself and its systems, as well as test results. These documents include:

- ✓ An Out of Specification (OOS) or Out of Trend (OOT) Investigation
- ✓ Raw material testing specifications, methods, and results
- ✓ In-process testing specifications, methods and results
- ✓ Cleaning verification
- ✓ Method validation data
- ✓ Equipment qualification
- ✓ Final release testing specifications, methods, and results for a drug product
- ✓ Release testing specifications for intermediates
- ✓ Personnel training records
- ✓ Analysts' laboratory notebooks
- ✓ Log books for equipment maintenance and calibration
- ✓ Log books for reference standards and preparations

### Data review

All data should be recorded in controlled notebooks, controlled worksheets, controlled files and/or validated computer systems (LIMS). Notebooks and/or worksheets should be properly signed and dated and concurrent with the tests being performed. If the laboratory

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equipment should be scheduled for preventative maintenance based on the manufacturer's suggested maintenance schedule and/or previous experience with the equipment. SOPs for calibration and maintenance should be reviewed to determine if they contain enough detail to ensure that equipment is operating with reliability and accuracy. The requirement for a calibration and maintenance schedule should be indicated in an SOP. If equipment is broken or needs repair it should be marked as "Out of Service", "DO NOT USE-repair needed" or other words that indicate the equipment should not be used. Calibrated equipment or instruments should have a visible sticker that indicates who performed the calibration, when it was performed and when the next calibration should be performed.

Computers or electronic Laboratory Management Information Systems (LIMS) used in the laboratory for databases, recording raw data and preparing reports, need to be validated. These same computers need to be fully compliant with Electronic records and electronic signatures requirements. Access to the computer and access to various types of information should be tightly controlled with the system available only to authorized personnel.

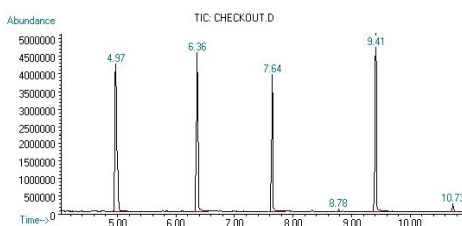
Spreadsheets used to perform result calculations or data interpretation need to be adequately controlled and validated. If there are any changes made to the hardware and/or software, changes must be made according to the change control system established at the site.

As an auditor, you will see many types of laboratory equipment and instrumentation. Some will be used to separate and quantify the components of the analyte or drug sample. Others will provide information about the chemical structure. Still others will be used to determine the physical properties of the drug product. A few of the more common methods and instruments will be shown below.

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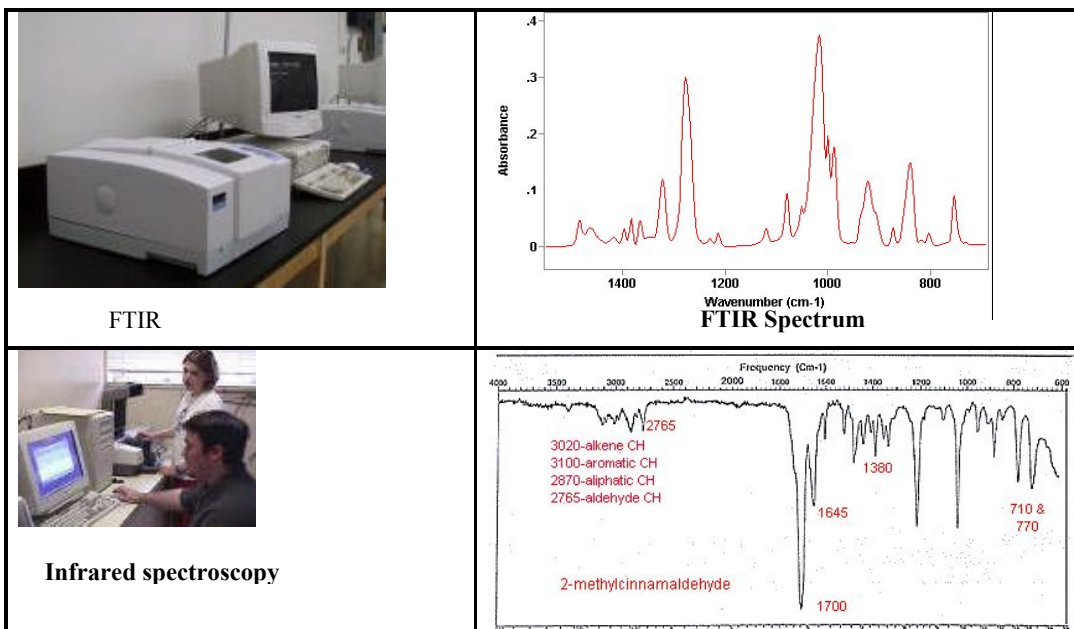
Gas chromatograph



Gas chromatogram

### Spectroscopy

Other tests that may be performed in the analytical laboratory are those that can identify functional groups on molecules. It is not unusual to take a sample from a separation method and then use another method to provide further characterization. Other instruments used are Fourier Transform Infrared (FTIR), IR, atomic absorption, mass spectroscopy and others. The results are printed as spectrum or spectra. In most instances the spectra will be plotted with the wavelength on the x-axis and the absorbance on the y-axis. Pictures of instruments with their spectra are shown.



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Change control procedures should also include directions for incorporating changes based on pharmacopoeia requirements and requires that the incorporation is timely.

### Stability Testing

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light. Stability testing permits the establishment of recommended storage conditions, retest periods, and shelf lives.

When a laboratory performs stability testing it must have an SOP managing all parts of the stability program. The SOP should include:

- Approved stability protocols specifying, at a minimum, sample size, test intervals, test storage, storage conditions as contained in the regulatory submission.
- A system for monitoring stability chambers
- A system for sampling stability inventory including specific times to remove and test stability sample.
- A procedure for reviewing stability data for trends
- An procedure for notifying management and performing investigations

Since monitoring of stability chambers is a high priority with regulatory agencies, the laboratory should use qualified chambers. These chambers should be assigned to a calibration and maintenance schedule. Temperature and humidity requirements should be established in an approved SOP. The chambers should have an alarm system and a procedure in place to manage both alarms and deviations. If there are any changes made to the chambers, the changes must be subject to the change control system established at the site.

Testing of the product should be performed in the equivalent container as clinical or market product, for development or commercial studies respectively. An adequate number of batches should be tested with stability indicating assays.

The site should also be monitoring laboratory results of stability test samples to determine if there is an OOT result. Trends may indicate a process drift and should be investigated and the cause determined. An approved SOP for defining what constitutes a trend and how to manage OOT results should be in place.

### Reserve/Retained Sample Testing

Samples of each lot in each shipment should be retained and stored in the same container-closure system under label conditions. The reserve sample consists of at least twice the amount required for full testing. Temperature logs should be maintained and available for review.

For API clinical trial material there should be system that ensures sufficient quantity of each reserved sample is retained for an appropriate length of time after approval, termination or discontinuation of an application.

Every year until discard, reserve samples or batches selected by acceptable statistical standards should be examined visually for evidence of deterioration.

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- SOPs/Quality Standards
  - Ensure that the current approved version is being used.
  - Ensure the analyst knows the correct test to run based on a Quality Standard.
  - Ensure that no uncontrolled documents or extract from SOPs or test methods are used.
  - Ensure all relevant procedures are available to lab personnel
  - Ensure that both test methods and specifications are available to laboratory personnel.
  - While observing an analyst, compare the test method being performed to the written version of the procedure.
  - Ensure that there is an approved change control procedure and a reasonable time frame for reviewing SOPs.
  - Ensure pharmacopoeia methods are verified for use in the laboratory.
  - Ensure that methods used are validated for their intended purpose.
  - Ensure that there are validation reports on file for the test methods.
  - Ensure that release methods include stability indicating assays.
- Reference standards
  - Ensure that a assigned purity is stated, where required and Certificate of Analysis for the standard is available in the laboratory.
  - Ensure that reference standards are stored under correct storage conditions.
  - Ensure that storage conditions are monitored.
  - Ensure that reference standards are within expiration date.
  - Ensure that standard preparations are labeled and stored correctly.
  - Ensure that storage time for standard preparations is valid.
  - Ensure that there are SOPs available for direction on handling and storing reference standards.
  - Review reference standard logbooks to confirm that the standards are being held under proper conditions.
  - Ensure there is a system in place for the traceability of reference standards.
- Reagents
  - Ensure that the grade of reagent is the same as specified in the regulatory submission.
  - Ensure that the reagent is properly labeled, stored, and has an assigned expiration/or re-assay date.
  - Ensure that the water used to prepare the reagent is of the purity required in the site SOP for preparation of the reagent.
  - Ensure that the lot number is recorded when a reagent is prepared.
  - Ensure that if water is held before preparing the reagent that there are scientific studies to justify the hold time.
  - Review reagent preparation logbooks.
- Volumetric Solutions
  - Ensure there is an approved preparation procedure in place.
  - Ensure that the data is recorded and easily accessible.
  - Determine what the expiration and re-standardization dates are.
  - Determine if they agree with the Pharmacopoeia
- Glassware
  - Ensure that Type A glassware is used for quantitative work.
  - Ensure that there are standard procedures in place for cleaning laboratory

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- Ensure that (in the case of a contract laboratory) the site practice is aligned with site requirements.
- Change Control Program
  - Ensure that methods, equipment, software and instrumentation are part of the change control program.
  - Ensure that appropriate approvals and levels of approval are in place.
  - Ensure that testing after the modification or change is performed.
  - Ensure the results are within the acceptance criteria.
- Personnel Training
  - Ensure that new employees, experienced employees and supervisors are fully trained/qualified.
  - Ensure that any contract employees(laboratory analysts, calibration and PM personnel) are fully trained and qualified to perform the assigned tasks.
  - Ensure that training requirements are defined in an approved SOP.
  - Ensure that laboratory personnel are receiving both GMP and job skills training and that it is documented.
- Equipment and Instrumentation
  - Ensure that equipment and instrumentation (including software) are qualified.
  - Ensure that equipment and instrumentation (including software) is part of a preventive maintenance schedule.
  - Ensure that stickers indicating maintenance dates or repair are current and that instruments not to be used are appropriately labeled
  - Ensure, upon completion of repair work, appropriate testing is performed as outlined in an approved change control program.
  - Ensure that the equipment list is accurate based on audit observations.
  - Ensure that all calibration procedures, whether internally or externally performed, have been approved by appropriate site personnel.
  - Ensure that calibration and maintenance is performed with sufficient frequency to assure optimal operating conditions of each piece of equipment or instrumentation.
  - Ensure that there are approved and followed SOPs for maintenance, calibration and change control.
  - Ensure stickers or systems are available to verify maintenance/calibration dates.
  - Ensure that all repair and maintenance work has been documented.
  - Ensure that reference weights used for control of balances are checked against national/international standards as appropriate.
- Test method validation
  - Ensure that test methods have been validated.
  - Ensure that there are SOPs directing the validation procedure/method.
- Stability testing
  - Ensure that there is an approved formal stability testing program in place.
  - Ensure the site is in compliance with pull dates from the stability testing program.
  - Ensure that stability test chambers and conditions have been validated.
  - Ensure that the testing performed for stability is appropriate and adequate.