Laboratory Testing for Compounding Pharmacies

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Sample Receipt and Accountability

- Ensure receipt of correct sample
- Log in sample- sample register or LIMS
- Sample quantity- rule of thumb, twice the amount to run all tests
- Uniquely identify sample in the laboratory- this would include glassware, HPLC vials containing sample solutions for example
- Sample tracking establishes “Chain of Custody”

21 CFR 211.194 (a)(1)

Laboratory Testing

- Tests should be conducted per validated methods, pre-approved by Quality Control Unit (QCU). QCU will be used synonymously with Quality Unit (QU) in this presentation.

- Information of samples, sampling, sample preparation and testing conditions, etc. should be documented and reviewed per SOP.

21 CFR 211.194(a)(2)
21 CFR 211.194(a)(3)

Method Verification/Method Validation/Method Transfer

Test methods and specifications should be developed based on USP, references from literature search or information of approved/marked products.

Laboratory should show that test methods are capable to perform tests and are fit for their intended use

21 CFR 211.194 (a)(2)

New methods should be validated. Elements for validation are provided by USP 1225, “Method Validation” and ICH Q2(R1), “Analytical Method Validation”. Generally, test methods should demonstrate:

Method Verification/Method Validation/Method Transfer

- Specificity
- Accuracy
- Precision
- Linearity
- Limit of Quantitation/Limit of Detection
- Range
- Robustness

Method Verification/Method Validation/Method Transfer

If methods are provided to a contract laboratory, there should be a formal transfer procedure for the receiving laboratory to demonstrate their ability to perform tests. USP 1224, “Transfer of Analytical Procedures”, provides types of method transfer:

- Comparative testing
- Co-validation between two or more laboratories
- Re-validation
- Transfer Waiver

The originating or developing organization should provide a preapproved transfer protocol, standards, test material, training (if necessary), the method and a transfer report.

Method Verification/Method Validation/Method Transfer

USP 1226, “Verification of Compendial Procedures”,

“Provides general information on the verification of compendial procedures that are being performed for the first time to yield acceptable results utilizing the personnel, equipment, and reagents available”.

“The verification process for compendial test procedures is the assessment of whether the procedure can be used for its intended purpose, under the actual conditions of use for a specified drug substance and/or product matrix”.

Stability Indicating Methods

For an assay method used to analyze a stability sample, it is essential that the method is specific as well as accurate. This means that impurities present in a chromatogram are resolved from the API peak. To optimize the separations of peaks, known impurities are spiked into the sample. The sample is also exposed to hydrolytic, oxidative, thermal, humidity and photolytic conditions, forced degradation studies, to produce additional chromatographic peaks to ensure separation from the active peak. Additionally, peak purity of the API peak is monitored to detect peak co-elution.

21 CFR 211.166 (a)(3)

Laboratory Document Management

- Documents used to capture raw data should be controlled by the QCU.
- Laboratory notebooks, usage logbooks and calibration logbooks should be permanently bound and issued the QCU with a unique identification.
- Worksheets should also be issued with a unique identification.
- A register of logbooks and worksheets should be maintained by the QCU to reconcile all documents issued.
- Maintain version control of SOPs, testing methods, OOS and deviation investigation reports; CAPAs, etc.

Data and Document Review

In-house laboratory

- Records should be filled contemporaneously.
- All entries should be signed and dated by operators/analysts contemporaneously.

21 CFR 211.194 (a)(8)

- Analytical results should be reviewed and approved by a designated responsible individual.

21 CFR 211.22 (a)

- The review should ensure that the correct sample was analyzed, the correct method used, standards and reagents were within expiry, equipment was within calibration/qualification, calculations were verified, review of instrument computer audit trails.

Data and Document Review

Contract Testing Laboratory (CTL)

Review if the CTL has SOPs to address above practices.

Request copies of documents from the CTL to demonstrate they follow these SOPs in practice.

- Applicable instruments and equipment should be qualified, calibrated and maintained per schedule.
- All relevant procedures, methods, and processes of the CTL should be reviewed and approved by the QCU.

Data and Document Review

- Changes in test methods, specifications, equipment or other contractual requirements should not be made unless the QCU is informed and approves the changes *(Note: A formal change control system should be established to evaluate all changes that could affect CTL services.)*
- Deviation from established procedures should be investigated and documented.
- Critical deviation investigations and conclusions should be communicated to the compounding pharmacy QCU per previously defined channels

Data and Document Review

- Other discrepancies, failures, OOS results, and OOT results in the CTL should be investigated, documented, and communicated to the compounding pharmacy QCU.
- Records should be kept at the CTL site where the activity occurs and is readily available.
- Auditing the CTL for compliance with CGMP, as defined in the written quality agreement

Reference Standards

- Qualified reference standards should be used for identification and quantitative analysis.

- A qualified reference standard may be a certified/primary standard or a secondary standard characterized against a certified/primary standard.

- Certificates of analysis (COA) of qualified reference standards should be maintained.

21 CFR 211.194(c)

Standard and Sample Solutions

Standard and sample solutions should be prepared fresh before use. If not, a solution stability study should be conducted if such information is not provided in the test method.

Out of Specification, Out of Trend and Laboratory Investigations

The laboratory should have a procedure to conduct investigations when an out of specification result is encountered. "The Guidance for Industry Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production", October 2006 described a two-phase investigation approach:

Out of Specification, Out of Trend and Laboratory Investigations

Phase I- Laboratory Investigation

Analyst Responsibility

- Instruments meeting established performance specifications
- Review data for accuracy
- Retention of standard and test solutions
- Obvious errors (e.g., spills, dropped autosampler vial)

Out of Specification, Out of Trend and Laboratory Investigations

Laboratory Supervisor Responsibility

- Timely assessment
- Discuss test method with analyst
- Examine raw data and calculations
- Confirm instrument performance
- Examine reference standards, solvents, reagents and other solutions
- Evaluate performance of the test method
- Document and preserve records of lab assessment

Out of Specification, Out of Trend and Laboratory Investigations

Phase II- Full Scale Investigation

Production Review

- A clear statement of the reason for the investigation
- A summary of the aspects of the manufacturing process that may have caused the problem
- The results of batch record review, with the assignment of actual or probable cause.
- Access batch record review to determine if the problem had previously occurred.
- A description of corrective actions taken.

Out of Specification, Out of Trend and Laboratory Investigations

Additional Laboratory Testing

- Retesting
  - additional weighing from original sample composite
  - re-injection
- Re-sampling
  - from original test composite or new sample collection

Reporting Test Results

- Averaging
- Outlier Tests

21 CFR 211.192

Laboratory Computer Systems

Validation and security of computer systems

- Access control-unique username/password
- Define user roles and limit system privileges
- Limit System Administrators
- Retain system validation documents
- Chromatographic data system audit trails enabled

Laboratory Computer Systems

Data Retention

- Periodic datafile backup
- Multiple back up copies; off site, fireproof safe

21 CFR Part 11-Electronic Records; Electronic Signatures

21 CFR 211.68 (b)

Laboratory equipment qualification/calibration

Calibration and maintenance program

- Frequency per manufacturer's recommendation (e.g., chromatographs, balances)
- Time of use (e.g., pH meters)
- Verification (e.g., verification weight checks: balances, system suitability: chromatographs)

21 CFR 211.160 (b)(4)
21 CFR 211.194 (d)


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