How to Conduct a Meaningful Laboratory Investigation -

& Create a Laboratory Investigation Checklist

SHABANA CHAUDHRY, CQA
This presentation is made at the request of IVT.

The information provided and opinions expressed during this presentation are those of the presenter and are not the position of and may not be attributed to Allergan, Inc.

The presenter is a full-time employee and stockholder of Allergan, Inc.
A growing number of 483s and warning letters being issued due to lack of investigations associated with the laboratory.

All test results that fall outside the specifications or acceptance criteria established in drug applications, drug master files, official compendia, or by the manufacturer.

Also applies to all in-process laboratory tests that are outside of established specifications.

211.160 & 211.165

Investigations should be “timely, unbiased, well-documented, and scientifically sound”

Patient safety
483s for Lab Investigations or “Lack of”

- There are many, some with no assignable cause

1. The Quality Control Unit failed to ensure that Phase I Laboratory Investigations were adequately investigated, documented, and trended after they were removed from the [REDACTION] system in September 2005 and transferred to a manual logbook.
   - The use of instruments and apparatus not meeting established specifications was observed.
   - Specifically, your firm failed to perform adequate investigations with scientifically justifiable conclusions to incidents of out-of-specification results or production deviations and/or failed to implement appropriate corrective actions for the root cause determination.

2. Drug products failing to meet established standards, specifications, and quality control criteria are not rejected.
   - Samples of drug products were routinely resampled, and re-injected or reprocessed in the [REDACTION] System during testing in the QC Laboratory when out of specification (OOS) results were obtained.
   - There were no Laboratory Investigations into OOS results or notebook documentation available to explain the re-injection or retesting of in-process, finished product and stability samples which did not meet specifications.

3. Your laboratory records did not contain all raw data generated during each test for API batches manufactured at your firm.
   - The investigator found that batch samples were routinely re-tested following failing or atypical results until acceptable results were obtained, and that failing or atypical results were not investigated or included in the official laboratory control records.
   - During the inspection, the presence of an uncontrolled “Custom QC laboratory” (CQC) was discovered by our inspection team. The existence of this laboratory was previously unknown to FDA. Your QC Associate Director acknowledged that the CQC laboratory was involved in CGMP analysis of APIs intended for export to the United States through 2012. This discovery was made one day before the end of the inspection, but during FDA’s brief evaluation of the high performance liquid chromatography (HPLC) electronic records generated by the CQC, our investigators found the following examples.
   - You performed assay/related substances by HPLC at (b)(4) on January 23, 2012. The sample failed the specification limit for purity, with a result of (b)(4)% (specification: NLT (b)(4)%). This failing result was not documented or reported. You repeated the analysis at (b)(4) on January 24, 2012, with a failing result of (b)(4)%. Again, you did not document or report it. On January 25, 2012, you conducted a third analysis at (b)(4). Your laboratory’s “Record of Analysis” for this batch, which you used to support batch disposition decisions, contained only the passing results obtained during the third and final test.
   - You conducted purity testing by HPLC at (b)(4) on January 27, 2012. This sample failed the purity specification limit (NLT (b)(4)%)) with a result of (b)(4)%, but you did not document, report or investigate the failure. Your QC data package, which you used to support batch disposition decisions, showed passing results from (b)(4) on the same day but does not include the initial failing results.
Laboratory Controls
CFR 211. 160 (a) Subpart I Requirements

- Establishment of:
  - Specifications
  - Standards
  - Sampling Plans
  - Test Procedures - SOPs must reflect actual practices
  - Other Lab Control mechanisms
  - Documented at the time of performance
  - Documented and justification for deviations
  - Test variability must be stated in advance
TESTING AND RELEASE FOR DISTRIBUTION
211.165 OOS (application) applies to:

- NDA
- DMF
- Official Compendia
- Manufacturer’s Specifications
- In-process Laboratory Tests
Roles and Responsibilities

- **Analyst**
  - Must report an OOS - out of spec. result
  - Must verify correct Procedure used
  - Must verify the equipment was calibrated
  - Supervisor be notified promptly

- **Other analyst**
  - Peer review
  - Conduct additional (independent) testing as procedure prescribes

- **Supervisor**
  - Must be involved
  - Must verify the procedure was followed
  - Must verify the specs. Are appropriate
  - Must consult with QA
Interpretation of Lab Data

- Breakdown of Lab Testing
- Basic Parameters to Investigate
  - Analyst
  - Equipment
    - Working Properly
    - Contamination
  - Supplies
    - Sampling Materials
    - Expired?
  - Environment
  - Controls
  - Changes (Vendor, Supplier, Type of material ex. glass vs. plastic)
  - Cleaning Procedures (if applicable)
  - pH
VALIDATION OF TEST METHODS

- SOPs - Are they following the procedure as written?
- Reproducibility
- Linearity (if applicable)
- USP Chapters:
  - <51> AET
  - <61> Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests
  - <62> Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms
  - <71> Sterility Testing
  - <81> Antibiotics Microbial Assays “Antibiotic Potency Testing”
  - <85> Endotoxin Testing
  - <1072> Disinfectants and Antiseptics
  - <1229.3> Monitoring of Bioburden
OOS/OOL/DEVIATIONS

- Alert and Action Limits
  - What action was taken when Alert Levels are reached?
  - Supervisor notified?
  - Closely monitored?
  - Low levels of contamination should be included in trend

- Importance of Sterility Test Results-Sterility Test Failures?

- Water System Investigations

- Adverse Trends (# of hits in X amount of time)

- Quarterly Reports

- Annual Reports

- Root Cause Analysis

- QA Involvement

- CAPA/Effectiveness Checks
CONTROLS

- Positive Controls are Positive
- Negative Controls are Negative
- Sterility
- Manual Test vs. Automated (System Suitability)
- In-House prep. Vs. Purchase Prepared
- Data Interpretation
- History
- Has anything been CHANGED?
  - Analyst
  - Supplier
- Missing Information= Invalid “If it wasn’t documented, it wasn’t done”
Other Possible Root Causes

- Personnel Hygiene
- Power failure
- Media
  - Evaluated for suitability for its intended purpose
- Calculation error
- Incorrect glassware used
- Sample temp. “Out of range”
- Wrong Test Method Used
- Atypical graph ex. Chemistry Chromatogram
- When should a lab investigation be initiated?
  - AS SOON AS POSSIBLE
  - Within 24 hrs.
  - Before anything is discarded
Definitions

- **OOS** - Out of Spec. - result that does not meet the **ESTABLISHED** registered/compendial **SPECIFICATION**
  - Action Level
- **OOE** - Out of Expectation - An atypical, aberrant or anomalous result within a series of results obtained over a short period of time is an OOE result. An OOE result is a result that meets specifications, but is outside the expected variability of the analytical procedure.
- **OOT** - Out of Trend - A reportable value that meets specs or action limits but is atypical or unexpected based on theory, process history, or known trends
  - Aberrant test results
  - fails a statistical process control criterion
  - OOA (Out of Alert) aka. OOL (Out of Limits) - internally set
  - Alert Level - tighter internal specs.
- **Control** - a sample or standard that is analyzed along with the test sample (being investigated) to verify analytical system and method are suitable
- **MDD** - Microbiological Data Deviations
- **Deviation from SOP** - Procedure not followed
- In ALL of these cases, should investigate
Repeat Testing vs. Re-testing

- **Repeat (Reassay)**
  - Is the same sample available for test?
  - Original sample prep.

- **Retain**
  - Was a duplicate sample taken?
  - Bioburden
  - Sample time/Same day
  - Refrigerated?
  - For info.

- **Re-sample**
  - Sample for confirmation
  - A different day/time
  - Next possible
  - New sample of the same batch

- **Retest**
  - A new preparation from the original sample container

- **Problems**
  - Destructive Tests

- **How many samples do you need for a retest?**
  - **Averaging**
    - 2,3,.....5 replicates
When should you escalate the issue?

- If no obvious lab error or root cause determined but recommend Supervisor involvement
- Analyst cannot disposition their own investigation
- Ex. Technician error Y/N
- Technician should not be the one to determine “no impact”
- CFR 211.100 b (Interpretations)
  - Deviations From Procedures
    - Explanations and approval are inadequate
    - Justification and approval are required
What is TMI (Too Much Information)?

- What not to say:
  - “Documentation error”
  - “This was not in the scope of our training”
  - “Lab contamination” “disregard” “entry error”
  - Changing results without justification
  - Facts only
  - Keep it simple- non-technical
Specs.

- Ensure that the specifications you are using have been validated/justified
  - Ex. Inhibition/Enhancement test
- Understand the limitations of the test
  - Ex. incubation times
- TRENDING
  - Only for Alert/Action levels?
- Averaging
  - More than one replicate required per procedure
  - Each replicate must be within established specs.?
  - The spec. is based on the average
Classifications of Investigations

- Simple
- Complex-inconclusive
- Phase I: Laboratory Investigation-Investigation performed between the initial Analyst and the Laboratory Investigator
- Phase II: Retesting and Resampling-If no obvious laboratory error is identified during the Phase I Investigation, conducted to determine the root cause of the initial OOS/OOT/OOA result.
TRAINING

- How to conduct an investigation
  - Consistency
  - Controlled Forms
  - Templates
  - GMP traceability - VERY IMPORTANT - printouts
  - Each step of the investigation must be fully documented...
  - Max. number of retests & repeat investigations should be specified

1. Analyst information
2. Data review
   - Review of product test history
   - Previous assay
   - Review of additional test results
   - Retest results
Phase I Investigation

- When can you invalidate a test result?
- If the analyst acknowledges he/she made a mistake or equipment malfunction-can terminate test
- Must verify that no obvious laboratory error occurred
- Lab error: A laboratory equipment error, analyst mistake or other laboratory process error that results in OOS/OOT/OOA.
- If all parameters investigated are within acceptable ranges
- Test is VALID

You can INVALIDATE a test if a root cause has been determined

- Technician Error
- Sample/Standard Prep.
- Analytical method
- Equipment Failure
- Controls ex. No growth on verification plates
- Recovery is within spec. ex. 50-200%
- Deviation from Procedure
Phase II

- Retesting and Resampling
- No obvious lab error
- May include any/all of these:
  - Retest
  - Reassay (repeat)
  - Resample
  - Control
- Performed by a DIFFERENT ANALYST
- Three times
- Confirming Integrity of the batch
- QA Involvement
- If OOS occurred at Contract Lab facility, then they must investigate per their investigation procedure
SAMPLE INTERVIEW FORM

Personnel Interview Form

- Investigation No: 
- Interview Plan: 
- Date: ______________

- Details of Interview (Who, What, When, Where, Why):
  Use Employee ID (not names)

- Interviewer Signature/Date:  Intervieweree Signature/Date:
- Title:  Title:
A BIGGER PROBLEM - Contamination

- Must determine the source
- Equipment should be quarantined
- Review sampling technique, sampling materials, sample location
- Cleaning and Sanitization
- Must prevent recurrence
- Microbial Identifications
- Risk analysis
FULL SCALE INVESTIGATION

1. A clear statement and reason of the investigation
2. A summary of the investigation of the manufact. process
3. Document Review - root cause or most probable cause
4. Recurrences - has this problem occurred previously - **VERY IMPORTANT**
5. List Corrective Actions

QCU is responsible for interpreting the results of the investigation/release batches

- Disposition - still may be released if determined to be unrelated to the manufacturing process and that (the quality of the batch is not compromised)
Exception Management

- Lab Investigations
- Production Investigation
- Root Cause Analysis
- Trending: monthly, quarterly, annually
- Training/Re-training
  - Too many documentation errors
  - How many times has the analyst actually performed the test?
- Effectiveness Check
Encarta defines “root cause” as the fundamental cause, basis, or essence of something, or the source from which something derives.

**What is Root Cause?**

*Root Cause* is the fundamental breakdown or failure of a process which, when resolved, prevents a recurrence of the problem.

Or, in other Words,

For a particular product problem, *Root Cause* is the factor that, when you fix it, the problem goes away and doesn’t come back.
Principles of Root Cause Analysis

- Focusing on corrective action of the root cause is more effective than simply treating the symptoms of a problem or event.
- RCA is performed most effectively when accomplished through a systematic process with conclusions backed up by evidence.
- There is usually more than one root cause for a problem event.
- The focus of investigation and analysis through problem identification is WHY the problem or event occurred, and not on who made the error.

The primary goal of using RCA is to analyze problems or events to clearly identify:

- What happened
- How it happened
- Why it happen, and
- Actions for preventing reoccurrence or established
Benefits of Using RCA

Traditional applications and benefits of Root Cause Analysis, include:

- Identify barriers and the causes of problems, to establish permanent solutions
- Resolution of customer complaints and returns.
- Disposition of non-conforming material (Scrap and Repair) via the Material Review process.
- Corrective action plans resulting from internal and customer audits.
- Identify current and future needs for organizational improvement.
DEVIATION MANAGEMENT

- Name of Investigator
- Who was involved?
- What (problem) occurred?
- Where it occurred?
- When it occurred?
- Product being processed/process being performed?
- How was it identified?
- What should have occurred?
- Initial actions taken
- Interviews
- Root Cause/Most probable root cause
INVESTIGATION CHECKLIST

Evaluation of Raw Data:
- System suitability acceptable?
- Standards/Controls results acceptable?
- Calculations verified and acceptable?
- Adverse trend observed?
- Anything unusual observed during testing (prep/analysis)?

Evaluation of Analyst:
- Training records verified?
- Has analyst performed this assay previously?
- Previous OOS with this analyst?

Evaluation of Analytical Procedure:
- Correct method no.?
- Current Version?
- Was procedure followed exactly?
INVESTIGATION CHECKLIST (continued)

Evaluation of Standards/Controls:
- Standard/Control condition acceptable?
- Standard/Control prepared per procedure?
- Standard/Control within expiration?
- Stored and handled properly?
- Dilutions performed correctly?
- Mixed correctly?
- Containers acceptable?
- Weighing performed properly?

Evaluation of Equipment:
- Equipment malfunction?
- Calibration verified and acceptable?
- PM verified and acceptable?
- Any error messages?
INVESTIGATION CHECKLIST (continued)

Evaluation of Sample:
- Sample condition acceptable upon receipt?
- Sampled prepared according to procedure?
- Sample tested within expiration?
- Were dilutions prepared correctly?

Evaluation of Reagents:
- Reagent(s) condition acceptable?
- Reagents prepared according to procedure?
- Reagents within expiration?
- Stored and handled properly?
- Used previously?
- Freshly prepared?

Data Analysis:
- Trends reviewed?
SUMMARY

- Investigations must be timely
- Analyst Responsibility to Escalate
- Supervisor Responsibility to Investigate
- QA Responsibility to release batch(es)
- Must review TRENDS on a regular basis as well as any previous OOS/deviations
- Must be FACTUAL and scientifically sound
- Investigations should include an RCA
- Develop an Investigation Checklist and templates
- Contamination issues must include quarantine of equipment and notification/production investigation
- BE AUDIT READY!
- Retrospectively, employ QBD
References

- Lee, John Y. Pharmnet “cGMP: Interpretation and Application” 10/1/2008
- Sutton, Scott PhD. “Successful Microbiological Investigations” American Pharmaceutical Review March 1, 2011
- USP <1117> “Microbiological Best Laboratory Practices” USP38-NF33 2015