Laboratory Audit Conduct
&
Corrective and Preventive Actions

Tobin Guarnacci
Global Head of Quality IVI

International Vaccine Institute

Auditing a Laboratory

Objectives

- Define a Clinical/Medical laboratory (CML) and differentiate between three (3) categories of laboratory practices
- Present the history and background of CMLs
- Describe CML, GLP and human Bioanalytical regulatory requirements and GCLP lab guidance (US NIH and WHO)
- Describe CML quality audit scope and conduct
- To describe CAPA basics, and CAPA response and management
- Describe applicability of the CAPA process to EQA follow-up for underperforming laboratories.

Auditing a Laboratory

What is a Laboratory Audit?

- A laboratory audit may be defined as a process of review and assessment of laboratory performance, and its purpose should be to improve customer/patient care by enhancing laboratory performance and making better use of resources.

- Audit is also an essential part of the quality assurance program of a laboratory which covers all aspects of the services provided. It may include policies on the induction and training of new staff, staff development, laboratory manuals, safety policies, equipment maintenance etc.

- An audit is a means of assessing whether one is achieving one's stated objectives.

Laboratory Types

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Auditing a Laboratory

What is a Clinical/Medical Laboratory?

<u>Clinical Laboratory</u> –

A facility for the biological, microbiological, serological, chemical, immunohematological, hematological, biophysical, cytological, pathological, or other examination of *materials derived from the human body for the purpose of providing information for the diagnosis, prevention, or treatment of any disease or impairment of, or the assessment of the health of, human beings*. These examinations also include procedures to determine, measure, or otherwise describe the presence or absence of various substances or organisms in the body. CLIA

Auditing a Laboratory

What is a Clinical/Medical Laboratory?

Medical Laboratory

A laboratory for the biological, microbiological, immunological, chemical, immunohaematological, haematological, biophysical, cytological, pathological or other examination of *materials derived from the human body for the purpose of providing information for the diagnosis, prevention and treatment of disease in, or assessment of the health of, human beings*, and which may provide a consultant advisory service covering all aspects of laboratory investigation including the interpretation of results and advice on further appropriate investigation. ISO15189 2012

Auditing a Laboratory

There are three (03) basic laboratory types and supporting regulatory requirements, accreditation requirements and Guidance

- Clinical/Medical Laboratory Regulatory Requirements and Standards
- Good Laboratory Practice (GLP) Regulatory Requirements and Standards (non-human bioanalytical analysis)
- Human Bioanalytical Laboratory Practice (GCLP) *guidance*

Auditing a Laboratory

What are Clinical/Medical Lab Requirements?

- Regulations, guidance and accreditation standards which define laboratory practices that support analysis and result reporting of *human samples* to medical professionals (e.g., Physicians) for the purpose of *diagnosis and/or treatment* of patients or clinical research subjects.

- The majority of testing methods employed in support of CML activity represent government approved in-vitro diagnostic devices (e.g., Approved by US FDA,CE marked in EU and MHLW/PMDA in Japan).

What is GLP?

- Regulations and guidance which define laboratory requirements which support *non-human* laboratory analysis for samples that are derived, primarily, from animal host systems.

- Non-human analysis supports *non-clinical (US FDA)/pre-clinical (OECD) research* studies.

Auditing a Laboratory

What is GCLP?

Bioanalytical *guidance* which defines laboratory practices that support analysis of *human research* samples which are *not* intended to be reported to medical professionals for the purpose of diagnosis and/or treatment.

What is GCLP?

- Human bioanalyitical analysis is typically used to support clinical research (GCP) and allow a sponsor of a clinical research study to evaluate *research* driven parameters (end-points) that may support safety and efficacy of investigational products (e.g., BE/PK samples, biomarker identification, etc.).

- Bioanalytical data may also be submitted to regulatory agencies to further support safety and efficacy or protocol driven investigational end points

Summary of Lab Categories

- CML applies to *human samples* for which results derived from analysis of such samples, will be reported to medical professionals (e.g., physicians) in support of diagnosis and/or treatment of patients;
- GLP applies to *non-human* samples which support non-clinical studies
- GCLP applies to bioanalytical analysis of human *research* samples in support of clinical studies for which results will typically *not* reported to physicians for use in diagnosis and/or treatment of patients (NIH and WHO)
- Korean MFDS has codified GCLP accreditation requirements for labs conducting human bioanalytical analysis in Korea supporting clinical research

Auditing a Clinical/Medical Lab

US NIH/DAIDS and WHO GCLP *guidance* documents were created to address a gap between bioanalytical labs supporting clinical research/GCP (i.e., labs analyzing human *research* samples) vs. GLP labs analyzing *non-human* research samples.

TABLE 1 – Categories of Laboratory Practices and Requirements/Industry Standards

APPLICABLE LABORATORY PRACTICE	LABORATORY CATEGORY	APPLICABLE REGULATORY REQUIRMENT OR STANDARD/GUIDANCE
Clinical/Medical Laboratory	Clinical/Medical Laboratory	•CLIA – 42 CFR 493 (US Mandated) •CAP Standards •ISO15189 •CPA (UK mandated for NHS laboratories based on ISO15189)
Good Laboratory Practice (non-human)	Non-clinical Laboratory/Pre-clinical (Bioanalytical Laboratory)	•21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies •OECD – Principles of Good Laboratory Practice and Compliance Monitoring
Human Bioanalytical Analysis	Bioanalytical Laboratory	•US FDA - FDA Guidance for Industry Bioanalytical Method Validation •EMA - EMA Guideline Bioanalytical Method Validation •MHRA Good Clinical Practice for Clinical Laboratories •Guideline on Bioanalytical Method Validation in Pharmaceutical Development (MHLW Japan) •GCLPs- NIH and WHO

AUDIT SCOPE and CONDUCT

Audit Scope and Conduct

- In order to define appropriate scope of any laboratory audit, the major phases of clinical analysis must be considered.
- These phases are well characterized by CLIA (US), CAP and ISO15189, and are applicable to GLP and bioanalytical laboratories

Audit Scope and Conduct

Phases of analysis:

- Pre-analytical/Pre-examination phase
- Analytical/Examination phase
- Post-analytical/Post-examination phase

Note: A failure of any one of these critical phases of clinical laboratory testing can significantly affect the integrity of a clinical result.

Audit Scope and Conduct

Pre-analytical/Pre-examination phase –

Represents all variables that can impact sample integrity *prior* to the analysis/examination phase.

Audit Scope and Conduct

Analytical/examination phase –

Represents all variables that can impact sample integrity and analysis *during* the testing phase.

Audit Scope and Conduct

Post-analytical/post-examination phase –

Represents all variables that can impact result reporting and follow-up.

TABLE 3 – Summary of Phases of Clinical/Medical Laboratory Analysis

CLINICAL LABORATORY ANALYSIS PHASE	VARIABLES IMPACTING PHASES OF ANALYSIS
Pre-analytical/Pre-examination phase	• Specimen transport and environmental control of shipping containers • Specimen requisition and accessioning • Analytical method and electronic system validation • Phlebotomy and sample collection methods • Sample storage • Interfering substances
Analytical and Examination phase	• Preparation of slides, solutions, calibrators, controls, proficiency testing materials, reagents, stains, quality of water and other materials used in testing • Definition of reportable ranges for test results (i.e., normal values) • References to manufacturer's test system instructions, package inserts and operator manuals • Identification of panic or alert values (as applicable)
Post-analytical and Post-examination phase	• Report formatting (i.e., electronic or paper formats which are associated with unique patient identifiers, laboratory identifiers, identification of test reference intervals and normal ranges) • Review, approval and release of result reports and corrected reports • Verification of accurate and timely final report receipt • Post-analysis sample storage and result retention.

Audit Scope and Conduct

Complexity of Testing and Regulatory/Standard requirements should be considered

- Waived – simple tests that do not require additional quality assessment (for a list of these tests, see www.cms.hhs.gov/CLIA/downloads/waivetbl.pdf
- Moderate Complexity – most automated tests that do not meet the waiver criteria
- High Complexity – non-automated tests (e.g., histopathology, Mohs surgery, cytodiagnosis of molluscum contagiosum, and microscopic hair shaft evaluation)

Audit Scope and Conduct

Auditor Selection –

- Auditors should be selected that possess practical laboratory experience
- Auditor qualifications and training should be documented
- Auditors should be vetted by an experienced peer before being allowed to conduct audits

Audit Scope and Conduct

It should be emphasized that laboratory audits should be conducted by experienced audit team proficient in the application of laboratory requirements or, at the very least, less seasoned auditors should be directed by an experienced team lead.

Audit Scope and Conduct

Basic Areas of Audit Assessment/Audit Scope:

- Quality Management, quality assurance and quality control
- Facility, Environment, Safety and Security
- Organization and Management
- Personnel, Orientations, training and Assessment
- Document Control/Standard Operating Procedures
- Method Validation, Validation
- Protocols and Reports
- Sample Shipping, Receipt, Processing
- Specimen Collection, Handling and Reporting
- Glassware, Quality of Water and Reagents
- Equipment Calibration and Maintenance
- Bioanalytical analysis (if applicable)
- Reporting of results
- Sample Management
- Electronic Systems
- Project/Study Management
- Data Management

Areas of assessment (1/7)

Quality Assurance/Quality Management

- ✓Does the laboratory have a documented quality management (QM) program which is integrated with the institutional program (as applicable)?
- ✓Does the laboratory summarize and review its records of errors and incident reports at defined intervals to identify trends and initiate corrective and preventive actions (CAPA) as appropriate (Complaints follow up and trending at defined intervals)?
- ✓Are key indicators of quality monitored and evaluated to detect problems and opportunities for improvement (e.g., turn-around-times)?
- ✓Are Preanalytical (e.g., order processing, specimen collection, transport), Analytical (e.g., sample receipt, processing, QC) and Post Analytic (e.g., turn-around-times and result reports) variables monitored?
- ✓Is the QM program appraised at least annually for effectiveness?
- ✓Does the Quality Assurance unit exist as a separate organizational entity?
- ✓Is internal auditing performed to confirm that the company's SOPs are being followed as written?

Areas of assessment (2/7)

➢ Facility, Environment Safety and Security

✓Formal, implemented and routinely tested Business Continuity Plan (BCP)?

✓Access control and monitor?

✓Fire / General safety?

➢ Organization and Management

✓Scope of operation

✓Org chart: The relations between the laboratory, management, technical operations, support services and the quality management system

➢ Personnel, Orientation, Training and Assessment

✓Training SOP and Records?

✓Employee competency monitoring?

Areas of assessment (3/7)

➢ Doc Control/Standard Operating Procedures (SOP)

✓Documented process for creating, reviewing, updating SOPs?
✓Training on new and/or renewed SOP for employees?
✓Deviation handling

➢ Method Validation, Validation Protocol/ Validation Report

✓What is the process for developing the validation protocol?
✓Does the Validation Report undergo independent review?

➢ Sample Shipping, Receipt/Processing What department is responsible for sample receipt?

✓Adequacy of reception and storage area?
✓Training on sample reception?
✓Documented tracking system to prevent loss of sample and ensure integrity?

Areas of assessment (4/7)

➢ Specimen Collection, Handling and Reporting

✓Sample collection manual: existence, reviews, approvals, training

✓Patient date protection?

➢ Glassware/Quality of Water/Reagents

✓Glassware inspection: cracks, contaminants, Interfering substances (e.g., detergent residues)?

✓Documented policy / procedure regarding water quality?

➢ Equipment Calibration and Maintenance

✓SOP on remedial action in case of equipment failure?

✓Is equipment adequately inspected, cleaned, maintained, and calibrated?

✓SOP and records on equipment maintenance and calibration?

Areas of assessment (5/7)

➢ Safety and Blood Borne Pathogens

- ✓Safety policy: availability, review, approval, implementation?
- ✓Accident reporting and recording?
- ✓Chemical Hygiene Plan?
- ✓Policy on hazardous waste disposal
- ✓Personal Protective Equipment
- ✓Sterilizing device monitoring with biological indicator
- ✓Material safety datasheet available?

➢ Conduct of a Bioanalytical Study (as applicable)

- ✓What is the process for developing the analytical protocol?
- ✓Who provides final review, approval and dated signature of the analytical protocol?
- ✓Does the final analytical protocol undergo independent review prior to sample analysis?
- ✓Training on the analytical plan?
- ✓Data recording practice

Areas of assessment (6/7)

➢ Quality Control (QC)

✓Written QC program?
✓How is QC material prepared?
✓QC trending analysis?

➢ Reporting of Bioanalytical study results

✓Independent review on analytical report?

➢ Sample Storage and Inventory

✓Sample storage tracking and inventory system?
✓Temperature monitoring on storage units?
✓Procedure for faulty storage units?
✓Storage unit maintenance?

➢ Storage and Retrieval of the Record and Data

✓Archival practice of raw data, documentation, analytical plan and final reports?
✓What is the record retention time?

Areas of assessment (7/7)

➢ Electronic Systems and IT

✓Is the computer system validated (e.g., LIMS)?

✓Is there a 21 CRF Part 11, Annex 11, GAMP5 (or equivalent) assessment for all computerized systems?

✓Is there an audit trail that captures additions, deletions and modifications of data?

✓What is the backup procedure?

✓Disaster recovery plan?

➢ Project Management/Study Management

✓What project management tools are used to manage the study?

✓Trial Master File or Project Documentation - How (and at what frequency) does the Organization ensure that all documents in the files are current and complete?

➢ Data Management

✓Case Report Form?

✓Data management: plans created and approved?

✓Do procedures exist for Coding (e.g. MEDRA and WHO Drug) and management?

Areas of assessment (7/7)

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Audit Scope and Conduct

Electronic Systems Controls and SW Validation (LIMS/LIS) (CAP LIS/Computer Procedure Manual and ISO15189 Appendix B)

- Procedures must be developed in support of all aspects of electronic systems and SW validation (e.g., change control, system development/maintenance, version specific user's manuals, back-up and restore process)
- Ensure that on-site servers are contained within a controlled environment (e.g., secured, temperature and humidity controls, fire suppression, appropriate power supply and back-up power, etc.)
- Ensure Software systems, either Commercial Off the Shelf (COTS) or internally developed systems, have been subject to appropriate validation.

Audit Scope and Conduct

Method Validation Requirements

Due to time constraints related to CML audit conduct, auditors do not (typically) have time to perform a detailed review of method validation

Critical aspects of method validation should be reviewed to include:

- Review of the method validation plan/summary report to identify acceptance criteria (e.g., acceptable ranges of analysis)
- Review of descriptive statistics generated in support of the validation plan/summary report requirements (e.g., regression plots, SD, %CV)
- Review of correlations studies comparing performance of redundant analyzers
- Review of raw data supporting calculations
- Ensure all documentation support method validation is associated with review and approval signatures (to include Lab Director and Lab QA)

Audit Scope and Conduct

***Method Validation Requirements/Method Performance Specifications *CLIA (42 CFR 493.1253)* and *ISO15189 (Sections 4.6.2, 5.3.2, 5.5.2 and 5.8.13)* state a CML must:**

- Verify analytic accuracy and precision
- Verify and document analytic sensitivity (lower detection limit)
- Verify and document analytic interferences
- Verify reportable range (Normal and reference range)
- *Not applicable to Waived Tests

Audit Scope and Conduct

Proficiency Testing (PT)
(CLIA 42 CFR 493.901, 903, 905 and ISO15189 ISO/IEC Guide 43-1)

- *PT is defined as determination of laboratory testing performance by means of interlaboratory comparisons, in which a PT program periodically sends multiple specimens to members of a group of laboratories for analysis and/or identification*
- *The program then compares each laboratory's results with those of other laboratories in the group…or more simply put…PEER ANALYSIS.*

Audit Scope and Conduct

Proficiency Testing (PT)
The following is required of a CML

- The laboratory must have written procedures for the proper handling, analysis, review and reporting of proficiency testing materials.
- A policy that prohibits interlaboratory communication about proficiency testing samples until after the deadline for submission of data to the proficiency testing provider
- Policy that prohibits referral of proficiency testing specimens to another laboratory.

Audit Scope and Conduct

Proficiency Testing (PT) –

- CML Samples must be tested in the same manner as routine samples

- PT samples must be tested for all high and moderate complexity tests within a CML (Defined in 42 CFR 493 Subpart I).

Audit Scope and Conduct

Proficiency Testing (PT)

What Constitutes Unsatisfactory Performance?

- Unsatisfactory performance for the same analyte in two consecutive or two out of three testing events.
- Repeated unsatisfactory overall testing event scores for two consecutive or two out of three testing events for the same specialty or subspecialty.
- Satisfactory performance requires that 80% of a participating laboratory's test results fall within a specified range of analytical precision

Audit Scope and Conduct

Equipment Maintenance and Calibration

All calibration dependent equipment must be traceable to an National Institute of Standards and Technology (NIST) or equivalent http://www.nist.gov/index.html (Equivalent standards can be supported by country specific Metrology agencies)

Procedures must exist defining calibration frequency and method for all calibration dependent devices (e.g., thermometers/probes, centrifuges, balances, and micro-pipettors, etc.)

Audit Scope and Conduct

Employee Training and Qualifications (CLIA 42 CFR 493.1351 to 1495 and ISO15189 Section 5.0) review of

Organizational chart

Review CML required qualifications (e.g., CLIA or country specific requirements)

- Laboratory Director
- Technical Supervisor(s)
- General Supervisor(s)
- Testing Personnel
- Clinical/Technical Consultants

Auditor must sample education, training and competency assessments

Audit Scope and Conduct

Medical Device Reporting (MDR)

- CML must have a procedure for reporting device-related adverse patient events, as required by US FDA (Similar requirements exist in many countries and should be evaluated on a case to case basis)
- In-vitro diagnostics approved by US FDA (or CE mark) are either Class II or Class III medical devices and subject to US FDA required Medical Device Reporting

http://www.fda.gov/cdrh/mdruf.pdf

Corrective and Preventive Action (CAPA)

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TERMS

Definitions:

- **1.1** Auditor – trained professional or group of professionals that conduct a systematic and objective examination of a process or system against a known and pre- defined standard.
- **1.2** Auditee - Individual or organization which is subject to an audit
- **1.3** Corrective Action - Planned action taken to eliminate the cause(s) of an existing nonconformity, defect, or other undesirable situation in order to prevent recurrence.
- **1.4** Preventive Action – Planned action taken to eliminate the causes of a potential nonconformity, defect, or other undesirable situation in order to prevent occurrence.
- **1.5** Effectiveness Verification - The means by which effectiveness of corrective and/or preventive action implementation is verified by a documented and systemic process.
- **1.6** Isolated Audit Finding - An audit finding that can be attributed to an isolated error but does not reflect a systemic/system wide problem.

TERMS

Definitions:

- **1.7** Root Cause - is the basic cause of any undesirable condition or problem, which when eliminated or mitigated will prevent or significantly reduce the effect of the condition or problem.
- **1.8** Root Cause Analysis (RCA) - Is a structured approach utilized in the identification of the basic factor(s) that attribute to an issue(s) of non-compliance within a system (i.e., root cause(s)).
- **1.9** Systemic Audit Finding - Observations that define a systemic and/or recurring trend or pattern that can be attributed to a root cause(s)

Corrective and Preventive Actions

- *The CAPA process described will be directly applied to EQAS activities related to observations identified during laboratory audits and as an improvement tool for underperforming laboratories.*

Corrective and Peventive Action

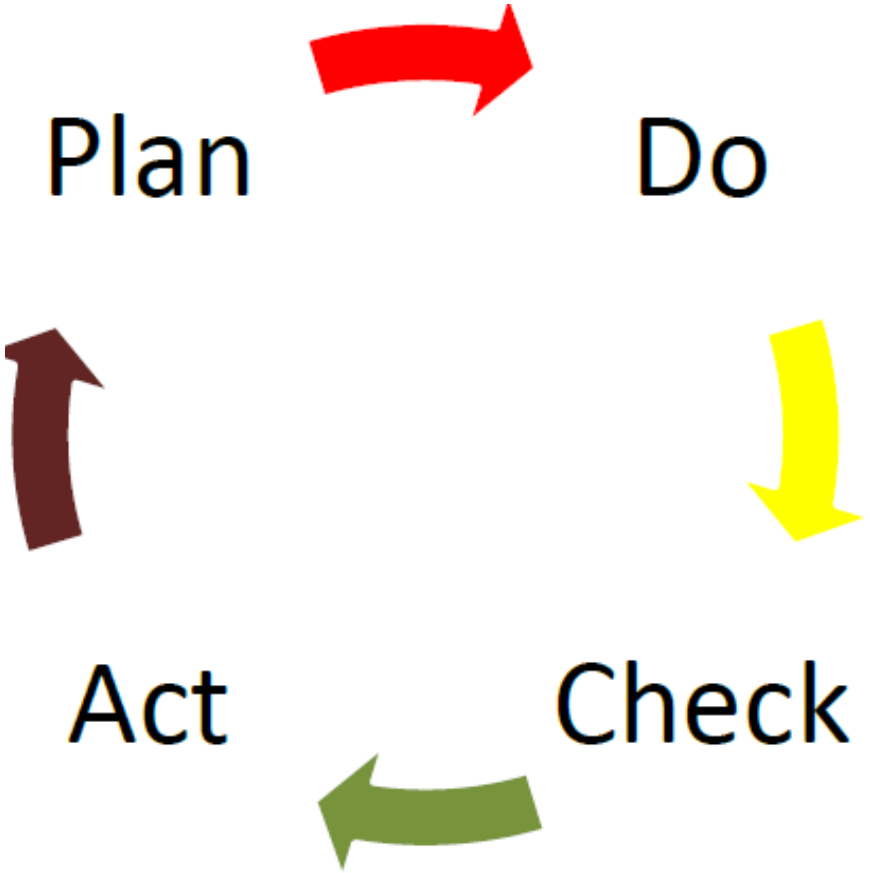
RESULTS OF AN AUDIT SHOULD **NEVER** BE USED BY MANAGEMENT FOR PUNATIVE ACTIONS

In other words, regardless of the severity of observations, an audit, internal escalation and resulting corrective and preventive actions (CAPA) should be used constructively as a tool for

- *Process improvement and compliance*
- *Personnel training and lessons learned*
- *Continuous quality improvement*

CAPA

Audit cycle / CAPA Cycle (CAPA is a sub-cycle of the report)



CAPA

Escalation of Audit Observations or Non-audit Related observations

- Audit Reporting and CAPA are a means of identifying and escalating significant issues of noncompliance that represent a departure from regulations/standards and that may impact compliance regulations/standards, patient safety and/or data integrity.

- Organizations should align identification and management of audit observations and escalation with a CAPA process as a means of ensuring that audit/non-audit observations are documented, tracked and effectively resolved.

CAPA

Auditor / Auditee /QM/ Stakeholder Interactions

- The most effective CAPA process is fielded by interactions between an organization's Quality Assurance/Quality Management (QA/QM) and the auditee or impacted stakeholder.

- Interaction with Quality Management (QM) should consist of guidance and support through discussion with the auditee/stakeholder (especially for auditees that are unfamiliar with a CAPA process).

- The QM should refrain from providing recommendations (i.e., defining the auditees CAPA responses) as this introduces bias into the audit process; however, QM should mentor and support stakeholders.

Note: the auditee/stakeholder is most familiar with systems and should better understand how to address issues of non-compliance. QM defining corrections/preventions may negatively impact both the auditee/stakeholder and QM.

CAPA

CAPA Initiation

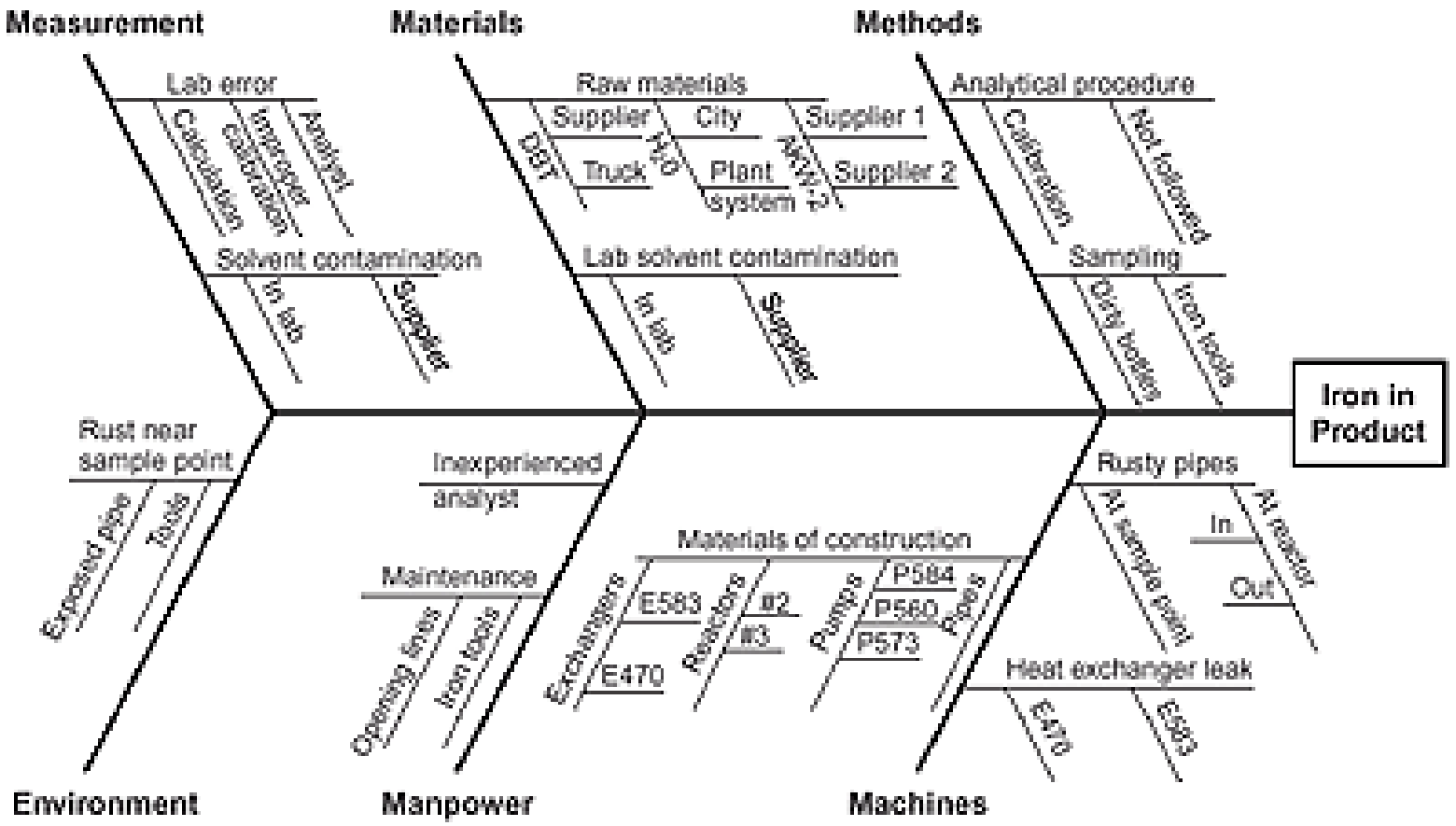
- The auditee or stakeholder begins initiation of the CAPA process in collaboration with QM (after an audit or when report of non-compliance is received by QM) by application of the following actions:
  - Auditee identification of root cause by performing root cause analysis (RCA) for each finding
  - Auditee defines corrective and/or preventive actions based upon root cause
  - Auditee defines timing of anticipated CAPA closure(s)
  - Auditor and auditee interactions supporting CAPA acceptance, effectiveness verification and CAPA closure.

CAPA

How to perform root cause analysis (RCA)

- **RCA is required to identify the basic cause(s) of any undesirable condition within a quality system. There are several techniques which may be utilized to assist an auditee in identifying root cause; two common and effective methods are:**
  - **Five (5) Whys Technique** -a question-asking method used to explore the cause/effect relationships underlying a particular problem. This method is effective in evaluating root cause relating to a single or less complex issue. Ultimately, the goal of applying the 5 Whys method is to determine a root cause of a defect or problem**.**
  - **Fishbone Analysis (Ishikawa Diagram) or Cause and Effect Analysis** - This method of RCA is useful in evaluating more complex/multi-factorial issues which have led to issues of non-compliance. The fishbone diagram identifies many possible causes of an effect or problem. It can be used to structure a brainstorming session as it allows a team of individuals to sort ideas into functional categories.

Fishbone Diagram



Ref: https://www.template.net/design-templates/print/sample-fishbone-diagram-template

CAPA

Identification of Root Cause (RC) and CAPA Implementation

- **Once RC is defined, the auditee proceeds to describe how corrective and/or preventive measures will be defined and applied to address the audit observation(s):**
  - Observations may require both corrective and/or preventive action
  - Observations may only require preventive measures (e.g., due to elapsed time of noncompliance it is too late to correct data)
  - Observations may only require corrective measures (e.g., isolated observations)

CAPA Responses and Timelines

- **Once CAPA response is complete, the auditee must then define timelines for the completion and closure of the CAPA.**
  - The auditee should ensure that realistic timelines for completion of the task at hand are described.
  - Often an inexperienced auditee will describe a time for completion of a CAPA that falls short of the actual time required for implementation. In this case, a member of the audit team may be needed to mentor and guide the auditee to an acceptable CAPA response related to timing.
  - Again, care should be taken to ensure that the auditor and audit team only advises and do not directly instruct the auditee, as this will introduce bias into the audit process.

CAPA

Effectiveness Verification (EV)

➢Once the auditor and the auditee have agreed that the defined CAPA and timelines for completion are acceptable to address the issue(s) of non-compliance, then the CAPA moves towards the final completion phase of the audit cycle: effectiveness verification.

•Effectiveness verification is the means by which effectiveness of corrective and/or preventive action implementation is verified by a documented and systemic process.

• EV may include the auditee providing documentation which describes evidence of action taken by the auditee which has resolved the audit observation (i.e., Documentation is provided to the audit team which reflects, to a reasonable degree, that actions taken by the auditee have effectively resolved the audit finding and that the issue will not recur).

CAPA Management and Tracking

- **To ensure all CAPAs are tracked to closure,**
  - Quality Assurance/Quality Management units should develop and implement a CAPA tracking system.
  - In many organizations this is linked to their audit management or compliance department systems and ensures that the CAPA and its status (e.g., open or closed) can be determined at any point to satisfy both organization management and/or regulatory agencies.

CAPA

CAPA Closure

- When all phases of the CAPA process have been satisfied through documented interaction between the auditor or auditor's organization (e.g., compliance unit's document control and management system) and the auditee; and the CAPA process and effectiveness of the CAPA have been confirmed, then the CAPA can be designated as closed.
- The auditor's organization and the auditee should both maintain records to support the CAPA effort in their official files.

Note: As CAPA documentation supports audit activity and defines audit observations, CAPA documentation should not be maintained in files with direct visibility to regulatory agencies.

EXAMPLE 1

CAPA Plan/Table Example

OBSERVATION 1 of 4 Classification: Audit Internal Escalation **Criticality: Critical Major Minor Opportunity for Improvement** **1. <Enter GXP Related Categories of Observation, e.g., Training and Qualification, IRB/IEC, etc.>**	
Observation: **<Enter general description of observation consistent with verbiage entered under "observations" in the audit report.>**	
Evidence/Comments:	
<Enter supporting evidence and detailed comments and examples related to the audit observation> **1.X** **a. X**	Response (please include date, initials and departme nt of responder with each entry): Root-Cause: Corrective Action (as applicable): Preventive Action (as applicable): Date of Projected Completion: Date Action Completed: Effectiveness Verification (QA USE ONLY): Responsible Person:
References: **•<Enter applicable regulatory requirements, SOPs, Industry Guidance, etc.>**	

EXAMPLE 2

Observations Criticality Designations:

Critical Observation	Observations that would be cited by a regulatory agency, which would have major impact on data credibility and may result in loss of part or all data and/or jeopardize subject safety. Study conduct will be impacted.
Major Observation	Observations that have the potential to be noted during a regulatory inspection and/or could result in the loss of some data or integrity of data and /or call into question subject safety. Study conduct will be impacted.
Minor Observation	Observations may be noted during a regulatory inspection. These deviations are not serious enough to jeopardize the data or subject safety but may impact study conduct
Opportunity For Improvement Observation	No regulatory deviations; however, generally accepted "industry standards/best practices" have not been followed.

Summary

Through the application of CML regulations and standards (e.g., CLIA, CAP and ISO15189), sponsors of clinical research will ensure the development of uniform and comprehensive processes which will allow for the identification and selection of proficient laboratory venders.

Summary Continued…

- Audit Reporting and CAPA are a means of identifying and escalating significant issues of noncompliance that impact compliance to regulatory/standards requirements, patient safety and/or data integrity.

Questions ?

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Questions and Answers

1. You are the quality manager in your laboratory, and you want to organize an internal audit. What steps would you take to organize the internal audit?

Answer

- Develop an annual audit plan (defining estimates for audit types (e.g., lab, vendor) and dates (e.g., Q1 2021, Q2 2021, etc.)
- Include laboratory management from the planning phase of audits and in collaboration with laboratory management, agree upon audit scope and dates for audit conduct.
- Send an audit notification/confirmation letter to the laboratory which includes dates of audit, audit scope and audit standards
- prepare checklist (audit tools) based on selected guidelines or standards
- Select auditors

Answer

- Conduct the audit and evaluate laboratory compliance based upon regulatory and accreditation standards. Data should be collected by the auditor through interviews, direct observation and document review
- prepare audit report and Corrective and Preventive action (CAPA) Plan/Table
- Present the report to management and the auditee
- Manage the CAPA plan/table to closure
- Complete the audit tracking and CAPA tracking spread sheets or enter tracking information in a validated electronic system.
- Retain the report and CAPA as a permanent laboratory record to be stored only in Quality Management files

Case study 2

2. Your laboratory participated in the EQASIA EQA pathogen identification and Antimicrobial Sensitivity Testing (AST) program. The results revealed several deviations (e.g., erroneous identification of pathogens, mis interpretation of AST result).

2.1 What steps will be taken to identify the root cause of the deviations?

Answer

- Examine and evaluate the condition of the sample when received and how it is handled.
- Evaluate compliance with procedures.
- Repeat quality control check on media
- Ensure reagents used are stored appropriately and are within the manufacturer's instruction
- Check equipment to be sure if it is properly calibrated and functioning well.
- Evaluate personnel competency.
- Carefully examine the reporting process, for example, checking for transcription errors.

Answer

Examples of the cause of errors follow:

➢ **Pre-examination**

- The sample may have been compromised during preparation, shipping, or after receipt by improper storage or handling.
- Improper sample management: identification problems, mislabeling.

➢ **Examination**

- The staff is not competent.
- Media used (purchased or in-house prepared), not well prepared, expiration date, properly sterilized and stored, PH, sterility was not checked, quality control was not performed
- Storage condition of the reagent (i.e., dehydrated media), antibiotic disc and quality control strains
- Equipment used for measurement and testing was not calibrated/maintained
- SOP not existing and/or not followed (test methods, quality control).

➢ **Post-examination**

- Clerical/transcription error

Answer

- **What corrective/ preventive actions might be taken?**
- provide training to the staff to assure consistent application.
- prepare/improve SOPs.
- prepare/purchase new reagents.
- improve/implement quality control.
- improves sample management process.
- Calibrate and maintain equipment used for measurement and testing

References and Helpful Links

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Title 42 US Code of Federal Regulations (CFR) 493 - Clinical Laboratories Improvement Act Clinical of 1988 (CLIA)
http://www.access.gpo.gov/nara/cfr/waisidx_04/42cfr493_04.html

International Standards of Operation (ISO) 15189:2007 (E) - Medical laboratories – Particular Requirements for Quality and Competence (www.ISO.org)

Clinical Pathology Accreditation (CPA) - http://www.cpa-uk.co.uk

Good Practices for Computerized Systems in GXP Regulated Environments
Microsoft Word - PI 011-3 Recommendation on Computerised Systems.doc (picscheme.org)

Clinical and Laboratory Standards Institute (CLSI) - http://www.clsi.org/

Asia Pacific Laboratory Accreditation Cooperation (APLAC)- http://www.aplac.org/

African Accreditation Cooperation (AFRAC)
http://www.intra-afrac.com

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http://www.european-accreditation.org/

CLIA Compliance Manual -
http://www.biomerieux-usa.com/upload/CLIA%20Combined-1.pdf

GLP

21 CFR 58 – Good Laboratory Practice for Nonclinical Laboratory Studies
http://ecfr.gpoaccess.gov/cgi/t/text/text-idx?c=ecfr&rgn=div5&view=text&node=21:1.0.1.1.22&idno=21

OCED – Principles of Good Laboratory Practice and Compliance Monitoring
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Draft Guideline on Bioanalytical Method Validation in Pharmaceutical Development (15 April 2013 MHLW Japan)
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References and Helpful Links

Bioanalytical (Clinical/Non(Pre)-clinical)

US FDA - FDA Guidance for Industry Bioanalytical Method Validation
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070107.pdf

EMA - EMA Guideline on Bioanalytical Method Validation
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/08/WC

MHRA GCLP Guidance -
http://www.mhra.gov.uk/Howweregulate/Medicines/Inspectionandstandards/GoodClinicalPracticeforClinicalLaboratories/index.htm

BARQA/RQA - GCLP, A Quality System for Laboratories which undertake the Analyses of Samples from Clinical Trials *http://www.barqa.com/cms.php?pageid=645*
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MHRA -
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US NIH DAIDs - http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2213906

World Health Organization - http://apps.who.int/tdr/publications/tdr-research-publications/gclp-web/pdf/gclp-web.pdf

General Links to Select Government Agencies

Sanitary Safety of Health Products Agency (AFSSAPS) of France - http://www.afssaps.fr/

US CMS – http://www.cms.hhs.gov/ContactCMS/

EMA European Union - http://www.ema.europa.eu

MHRA United Kingdom - http://www.mhra.gov.uk/index.htm

PMDA Japan - http://www.pmda.go.jp/english/

US FDA – http://www.fda.gov/AboutFDA/ContactFDA/default.htm

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Electronic Systems and Software Validation References

US Title 42 US Code of Federal Regulations (CFR) 493 - Clinical Laboratories Improvement Act of 1988 (CLIA) http://www.access.gpo.gov/nara/cfr/waisidx_04/42cfr493_04.html

US 21 CFR 11 – Electronic Records; Electronic Signatures http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?cfrpart=11

US FDA Guidance – General Principles on Software Validation or http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm126955.pdf

US FDA Guidance – Computerized Systems Used in Clinical Investigations http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.PDF

ISO 9001:1994 Quality Systems – Model for quality assurance in design, development, production and installation and servicing http://www.iso.org/

ISO 9126 - Standard Software Product Quality http://www.iso.org/iso/iso_catalogue/catalogue_tc/catalogue_detail.htm?csnumber=39752

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CAP Laboratory General Checklist

CLSI EP5-A2: Evaluation of Precision Performance of Quantitative Measurement Methods

CLSI EP6-A: Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach

CLSI EP9-A2: Method Comparison and Bias Estimation Using Patient Samples

CLSI EP10-A3: Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures

CLSI EP15-A2: User Verification of Performance for Precision and Trueness

Good Clinical Practice (GCP) and ICH-E6 (R2)