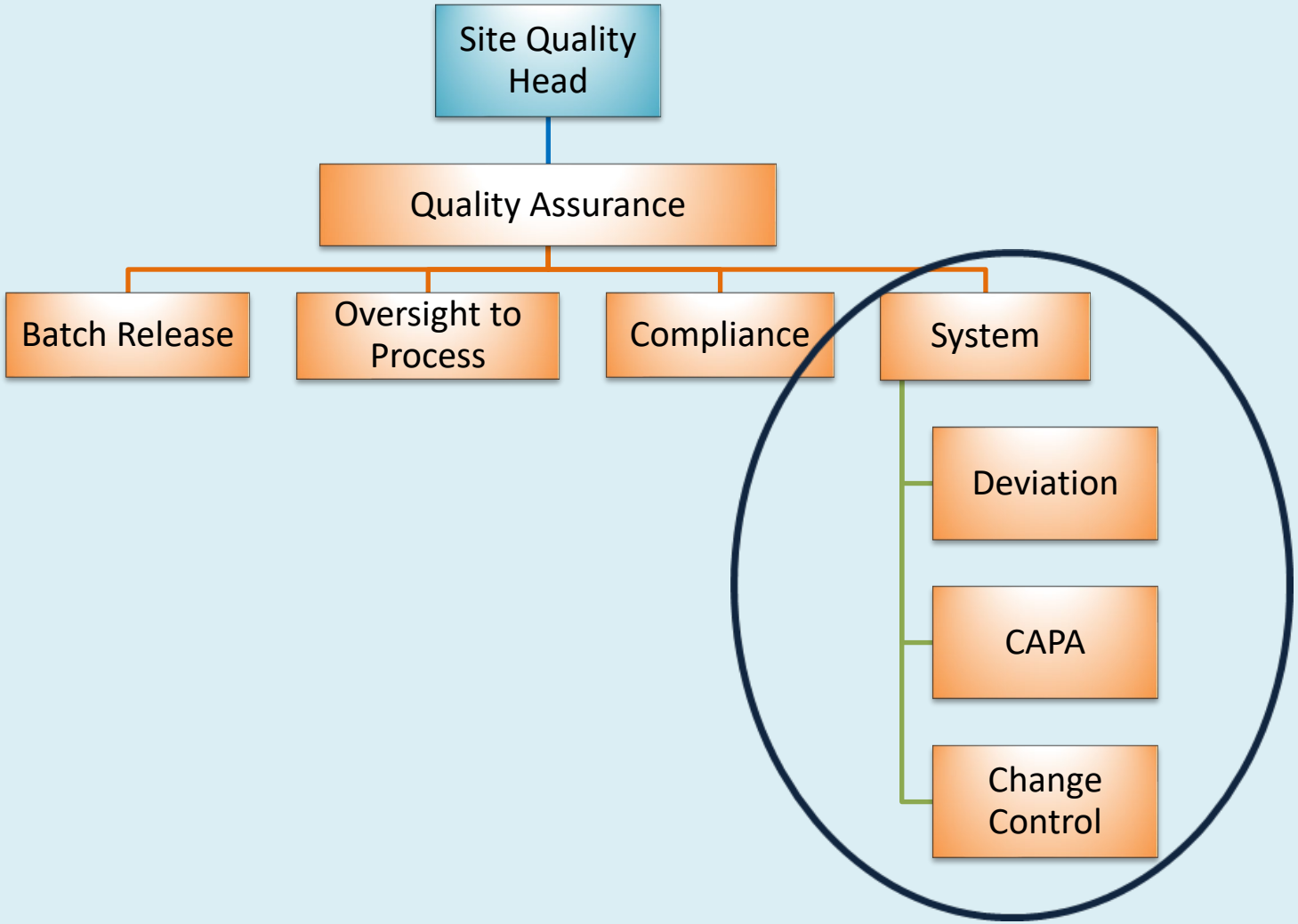
Quality System - Deviation

Learning Outcomes

- Concept of Deviation
- Components of Deviation Report
- Root Cause Investigation Methodology

Example of Quality Organization Structure



Deviation

- **Deviation** – *Any unplanned departure from approved instructions (e.g. SOP), established standards, specifications, batch records and other official GMP documentation. Non-fulfilment of GMP requirements*

- **Incident** – *Any unplanned event that is not part of standard operation*

- **Non-conformance** – *A deficiency in a characteristic, product specification, process parameter, record or procedure that renders the quality of a product unacceptable, indeterminate or not according to specified requirements*
  - Product non-conformance: product is out of specification (OOS)
  - Process non-conformance: process is not followed

- **Root Cause** – Reasons for resulting/attributing to the non-conformance of incident

Deviation

- When an **event** *(incident)* associated with manufacturing, processing, testing, packing, labeling, storage or distribution, occurs away from normal expectations *(non-conformance),* a **deviation** is said to have happened.
  - Deviations can also be defined as **atypical events** happening outside approved operating parameters or procedures
  - Many times, deviations require **manual intervention** to the affected process (eg stop the operation, make correction, arrest the leak etc).

- A deviation is required to be initiated by the discoverer or area owner, typically within 2 business days.

- Inform QA within the same working day of discovery to assess the atypical event in the affected department (eg manufacturing, warehouse, utilities area),
  - whether to classify it as a deviation
  - discusses the **potential impact** of the event on the quality attributes of the biologic medicine

Some Examples of Deviation, Incident & Non-Conformance

Manufacturing biotechnologist did not follow procedure from updated SOP

Bioreactor pressure readings were out of normal expected range

Unexpected failure of the centrifuge during upstream processing

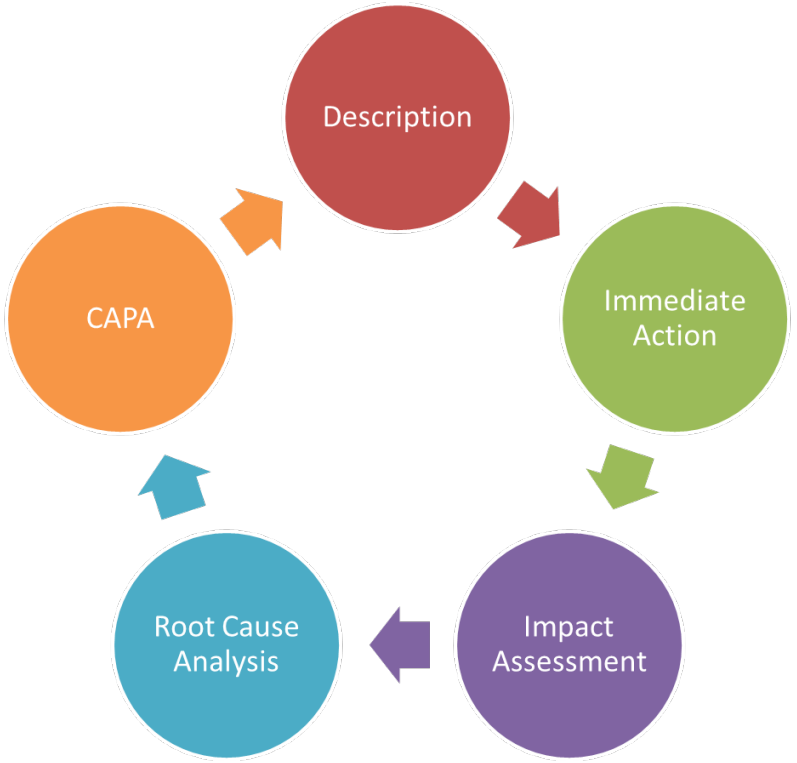
The final rinse samples from the CIP of a bioreactor tank are not meeting specifications (eg high conductivity readings due to traces of detergent)

Deviation

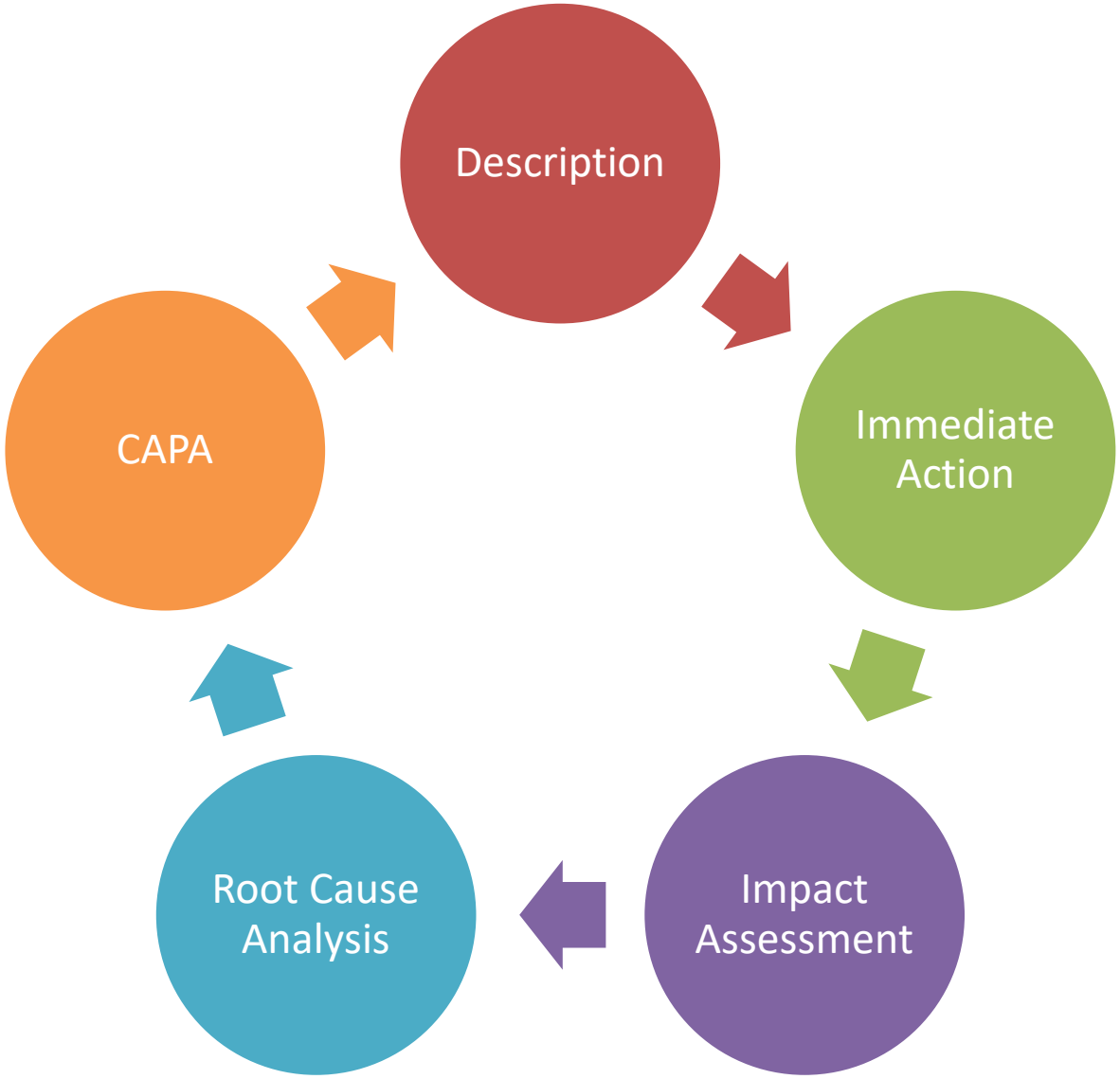
- Deviation is required to be **properly documented**. The deviation report is written by area owner and subjected to QA for review, approval and closure.

- The purpose of a deviation report is to provide documented evidence of the incident, assess product & process impact, identify the root cause and determine appropriate actions (CAPA) to re-gain control of the situation. It also serves to fulfil compliance requirement.

- Deviation reports should minimally comprise the following structure;



Deviation


Description
Immediate Action
Impact Assessment
Root Cause Analysis
CAPA

1. Description

Document the problem statement correctly in a timely manner.

An incomplete description will lead to a poor understanding of the problem and may result in ineffective impact assessment and root cause investigations. The description should be

- Clear and concise.
- Structured, using “what, who, where, when, how and how much (**4Ws2Hs**)”

The example for 4Ws2Hs are given as follows:

- **What**: The result of Calcium by Inductive-Coupled Plasma (ICP) method AM7006 for batch L826M773K was 99 mg/L , which is out of specification limit (OOS) of < 82 mg/L.
- **Who**:

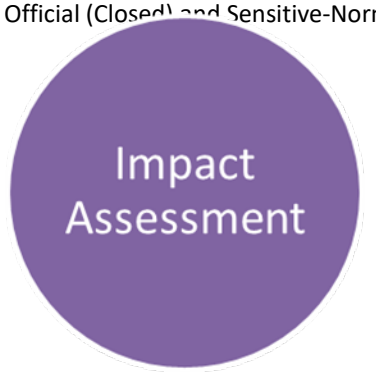
  Lilian Ng, lab analyst who involved in the testing

  Alex Khoo, lab chemist who involved in the review of lab results
- **Where** : The testing was performed in Chemistry Laboratory (CL-002).
- **When**:
  Occurrence date : 05-Feb-2022 (Date where OOS result was generated)
  Detection date: 07-Feb-2022 (Date where OOS result was discovered)
- **How**: The OOS high result was discovered during the review of lab results as per SOP-T336
- **How much**: Batch L826M773K

2. Immediate Action: Containment and Correction

- Identify what is immediately affected; **contain the event/problem and make corrections** where necessary:
  - If product is involved, identify and evaluate lots or batches run before and/or after the event under investigation.
  - Has any affected material been released or distributed to customers?
  - Determine what actions can be taken immediately to reduce risk to patients and company

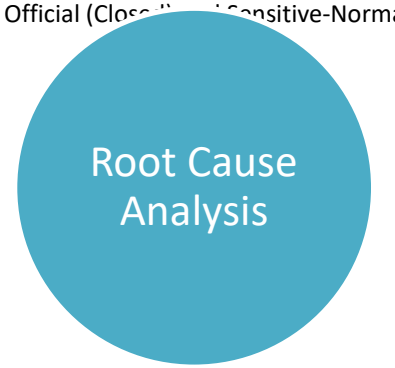
- Examples of immediate corrections:
  - Initiate QC laboratory investigation report
  - Stop the leak or clean up the spillage
  - Replace faulty equipment
  - Quarantine product
  - Recall product
  - Stop manufacturing (last resort)



3. Impact Assessment

Area to assess	Consideration Factors
Material/Product	**Impact to Quality, Safety, Purity, Efficacy & Stability**
Validation	Impact to **validated state** of process, analytical testing , equipment and etc
Regulatory	Impact to **regulatory filing** (e.g. the non-conformance is outside the filed registered range?)
Process	Impact to **process continuation** (e.g. Is the process able to resume or need to terminate)

Based on the above, make a disposition recommendation on the impacted batch: Lot **release**, **discard** or even **recall**



4. Root Cause Analysis

Conducting an Investigation

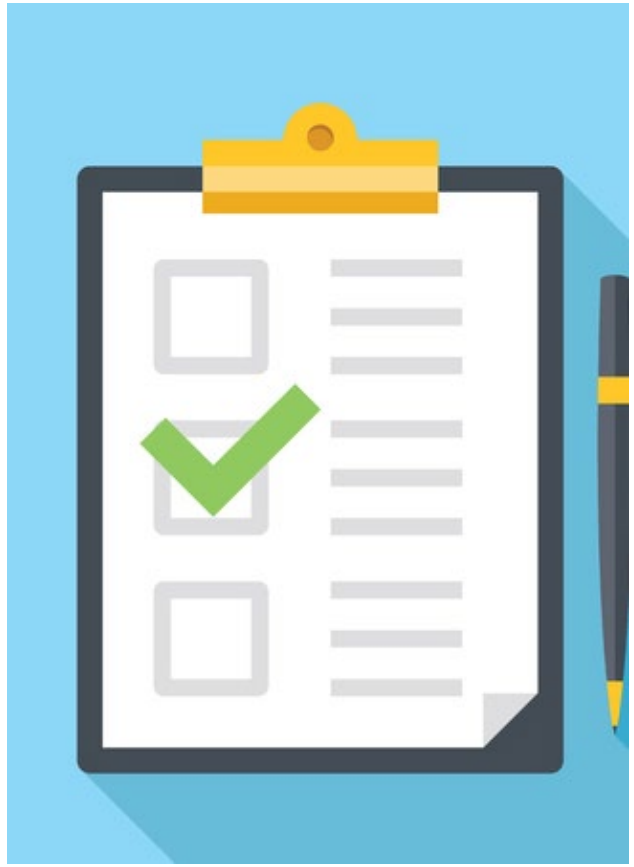
Possible actions to perform as part of root cause investigation:

- Review related records and documents (e.g. MBR, logbook, FORM and etc)
- Interview involved personnel (e.g. biotechnologist, lab analyst)
- Gemba Walk: Perform walkthrough at the affected areas, observe operations; inspect/test products, materials, equipment and facilities
- Hypothesis testing, experimentation or simulations
- Evaluate if there is any changes or anomalies occurred
- Identify if this is a recurring trend

Root Cause Analysis

Root Cause Investigation Methodology -

Laboratory Investigation Checklist



- Checklists are beneficial in providing a standard, consistent list of potential sources of error. For example:
  - Was the correct procedure followed?
  - Was the person trained in the procedure?
  - Does the procedure match actual practice?
  - Is this a recurring issue?
  - Was there an equipment problem?
  - Was the equipment calibrated?

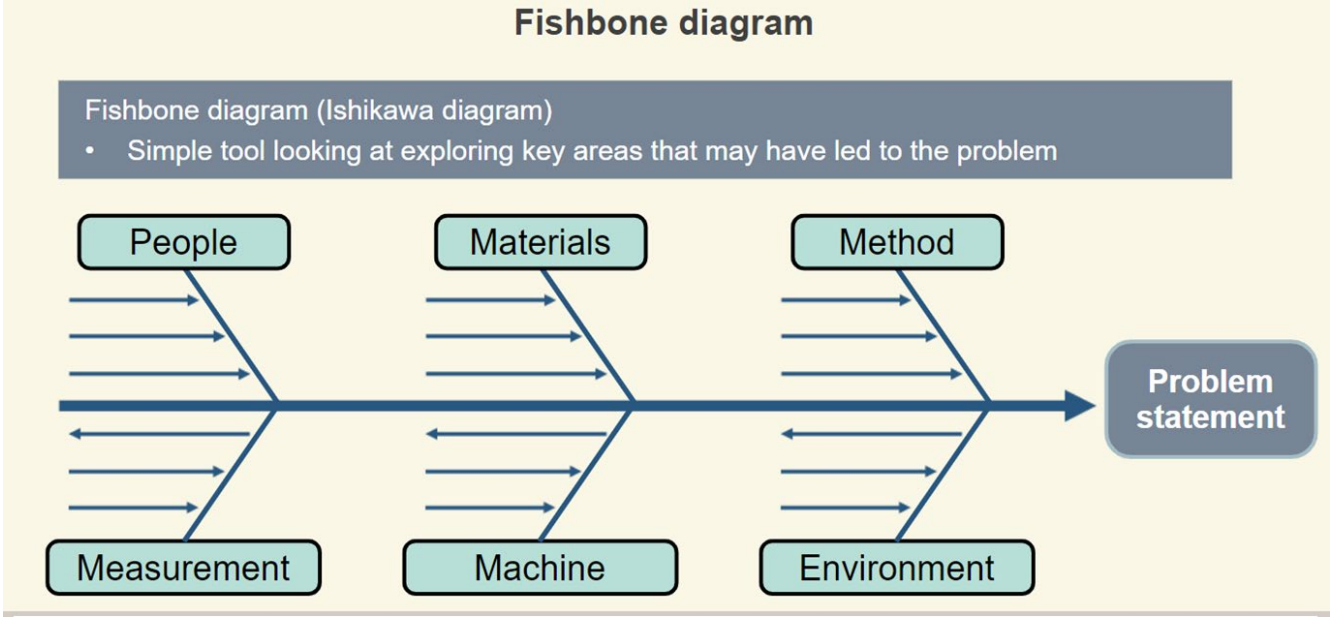
- If the checklist does not identify the root cause, there are a number of other tools that you can use.

Root Cause Analysis

4. Root Cause Analysis

Root Cause Investigation Methodology - **6M**

Cause-and-Effect Diagram (Ishikawa Diagram/ fishbone) - Provide a visual structure of all of the possible causes related to the problem into 6 major categories



Root Cause Analysis

Man

- Training status
- Distraction – multi tasking
- Gowning

Material

- Reference Standard
- Reagent
- Apparatus / Tools
- Expiry date
- Storage

Method

- Method validation status
- SOPs
- Forms
- Checklists
- Non documented way of working
- Specifications

Measurement

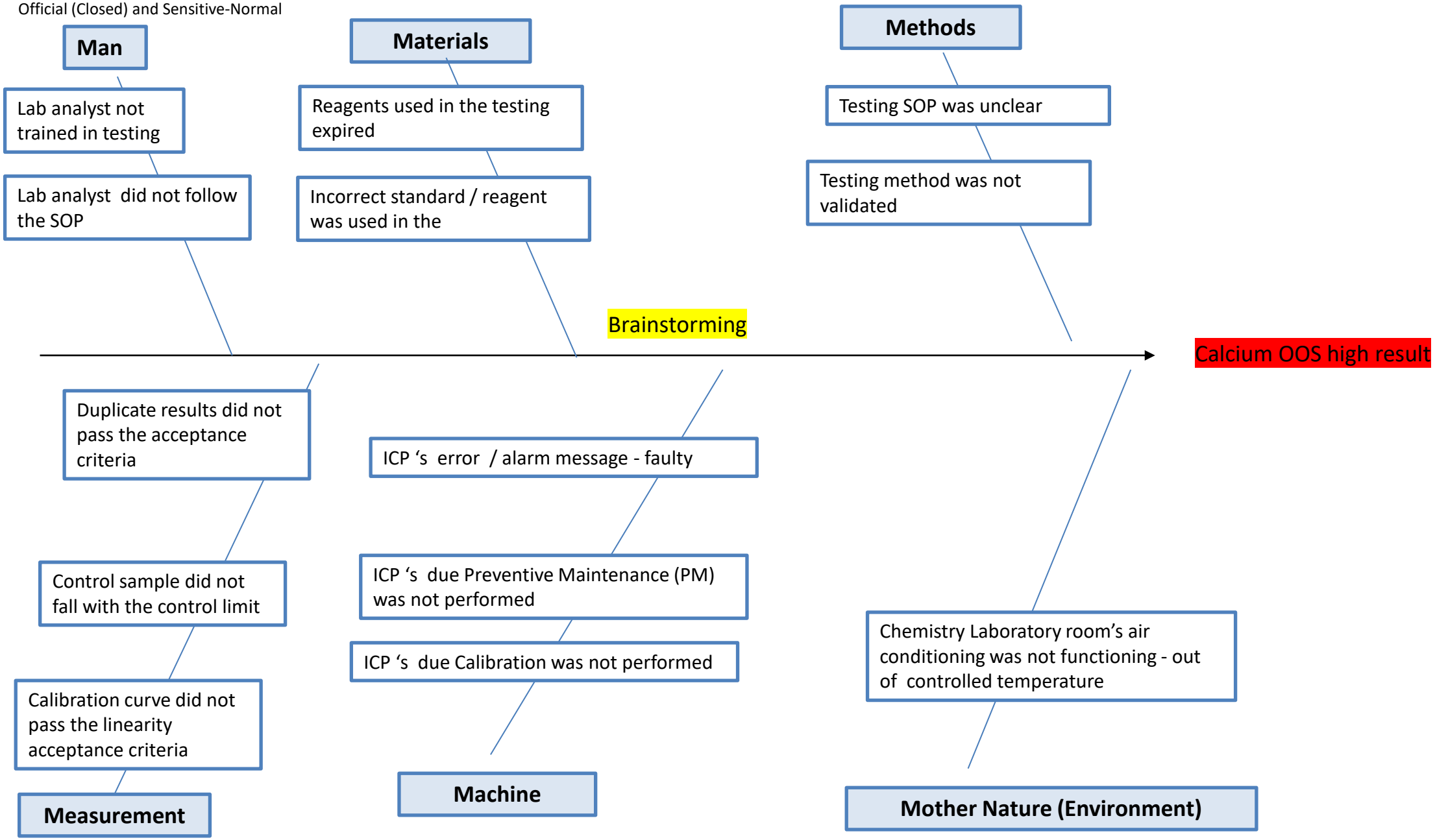
- System suitability - Linearity, control limit, repeatability

Machine

- Validation status
- Requalification status
- Design of equipment
- Maintenance & Calibration
- Cleaning status & frequency
- Functionality

Mother Nature

- EM monitoring data
- Temperature, humidity, pressure differences

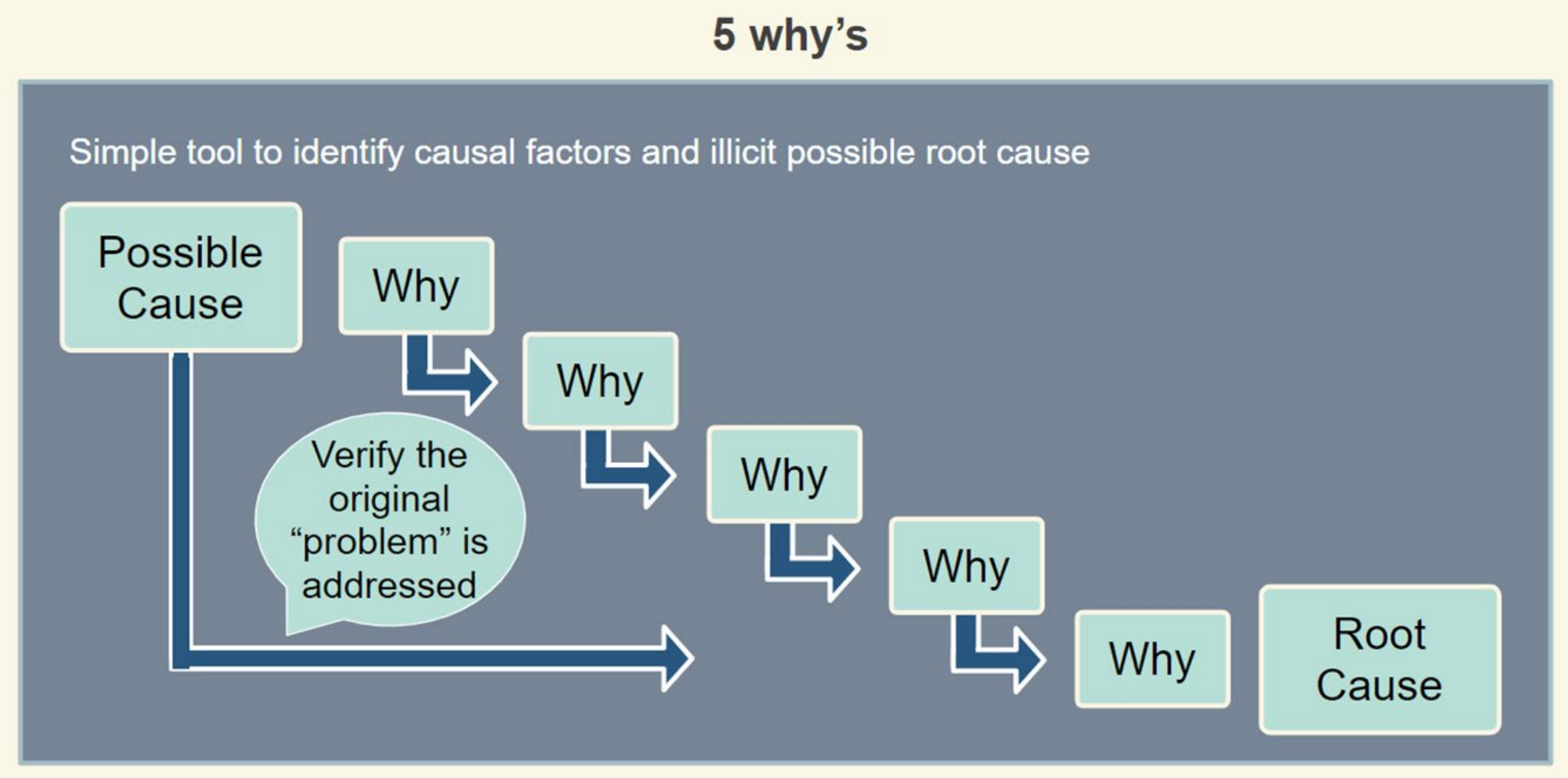


Root Cause Analysis

Root Cause Analysis

4. Root Cause Analysis

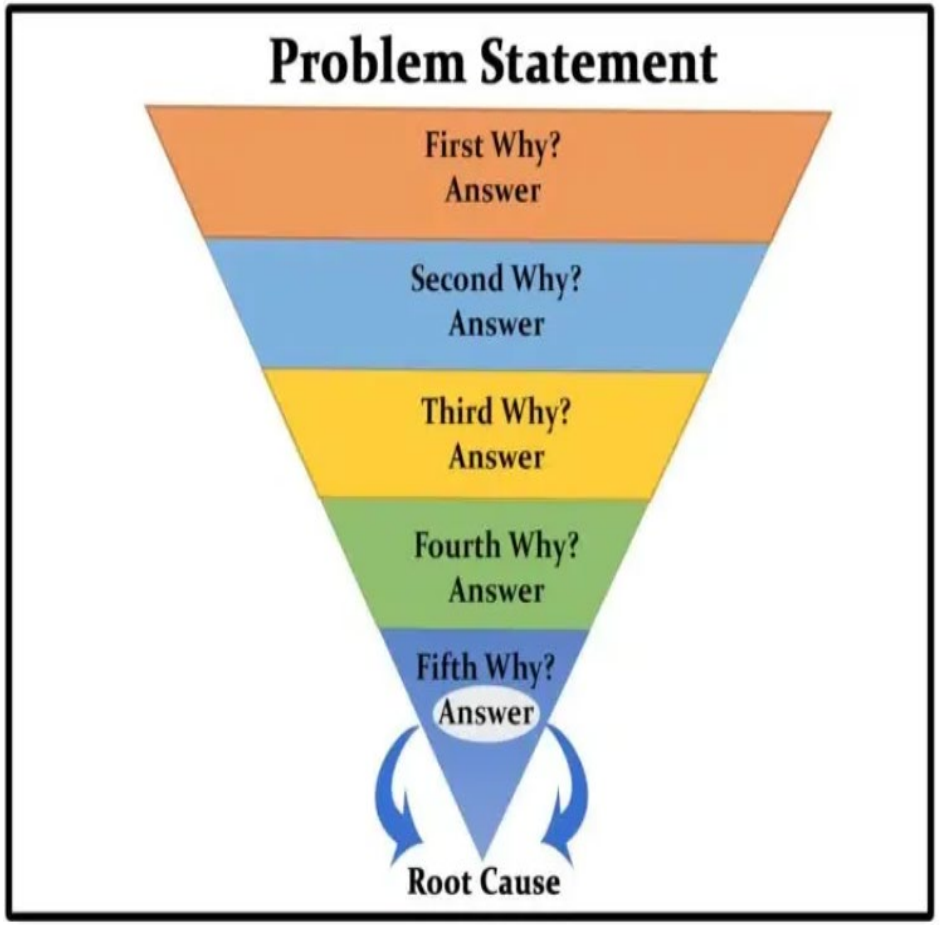
Root Cause Investigation Methodology - **5 Why's** - identify the real root cause of an issue by asking Why for about 5 times.



Root Cause Investigation Methodology - 5 Whys

Root Cause Analysis

Water sampling was performed in point A (W001-002A) instead of point B (W001-002B)



Root Cause: Inadequate line tags system design

Why was incorrect sampling performed?

Operator was confused in the sampling points

Why was operator confused?

There are too many water lines with similar line tag in the utilities area (e.g. W001-002A vs W001-002B)

Why are there having similar line tags?

The line tags are not distinguished clearly for easy differentiation?

Why are there not having line tags for easy differentiation?

The line tags systems lack of colour coding system?

What does the line tags systems lack of colour coding system?

The line tags systems design does not include colour coding system.