Conducting Quality Investigations

Panelists:
Scott Soukup, Quality Specialist, RCA Inc.
Joan M. Ward, Quality Subject Matter Expert, RCA Inc.
Susan Schniepp, RCA Distinguished Fellow, RCA Inc.

Moderator:
Debra Kurtz, President, Kurtz Consulting Inc.

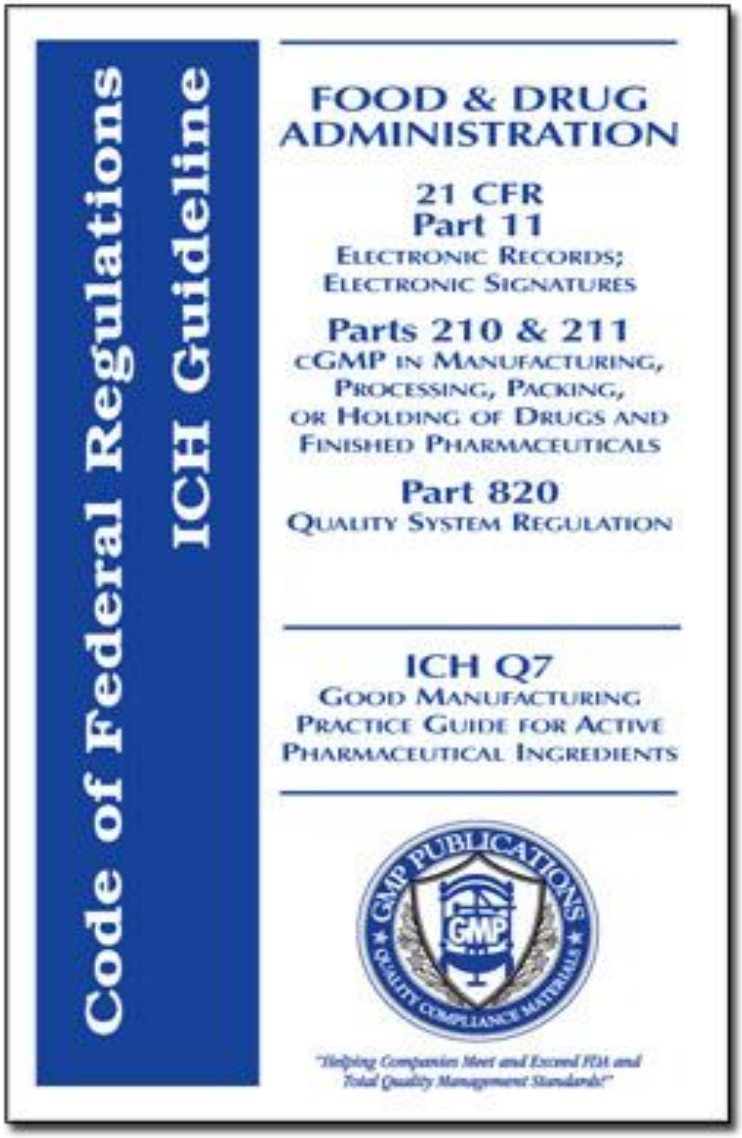



Agenda

- Why do we investigate?
- When do we investigate?
- How do we investigate?
- Case Study
- Summary
- Q&A

Why? (cont.)

- Required by law
  - Food, Drug and Cosmetic Act
  - 21 CFR 211.22
  - 21 CFR 820
  - EudraLex
  - ISO 13485

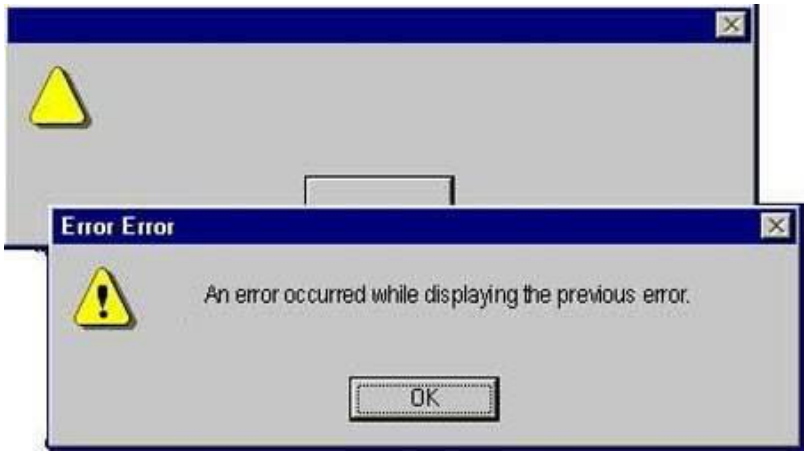


Food, Drug and Cosmetic Act

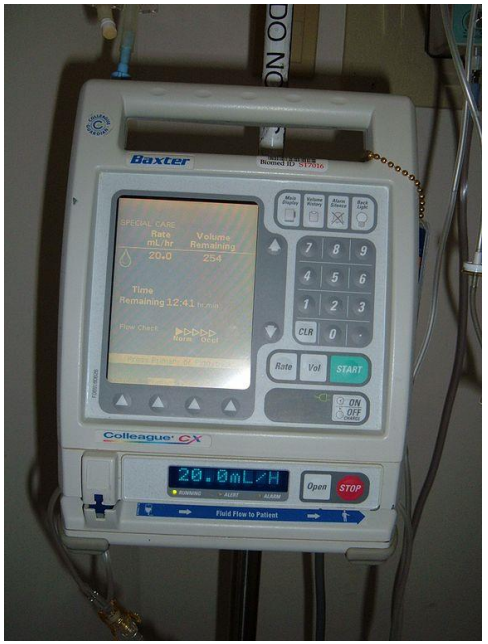
- SEC. 501. [21 USC § 351] (a)(2)(B)
  - a drug shall be deemed to be adulterated if **the methods used in**, or the **facilities or controls used for**, its **manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice** to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess.

21 CFR 211.22

(a) There shall be a quality control unit that shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, **if errors have occurred, that they have been fully investigated.** The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company.



21 CFR 820



- 820.100: "Investigating the cause of nonconformities relating to product, processes, and the quality system"
- 820.198: "Any complaint involving the possible failure of a device, labeling, or packaging to meet any of its specifications shall be reviewed, evaluated, and investigated."
- 820.90: "The evaluation and any investigation shall be documented."

EudraLex Volume 4

- A Pharmaceutical Quality System appropriate for the manufacture of medicinal products should ensure that:
  - The results of product and processes monitoring are taken into account in batch release, in the investigation of deviations, and, with a view to taking preventive action to avoid potential deviations occurring in the future.
  - An appropriate level of root cause analysis should be applied during the investigation of deviations, suspected product defects and other problems.
  - Appropriate corrective actions and/or preventative actions (CAPAs) should be identified and taken in response to investigations.
  - A review of all batches that failed to meet established specification(s) and their investigation.
  - A review of all quality-related returns, complaints and recalls and the investigations performed at the time.

ISO 13485

International Organization for Standardization

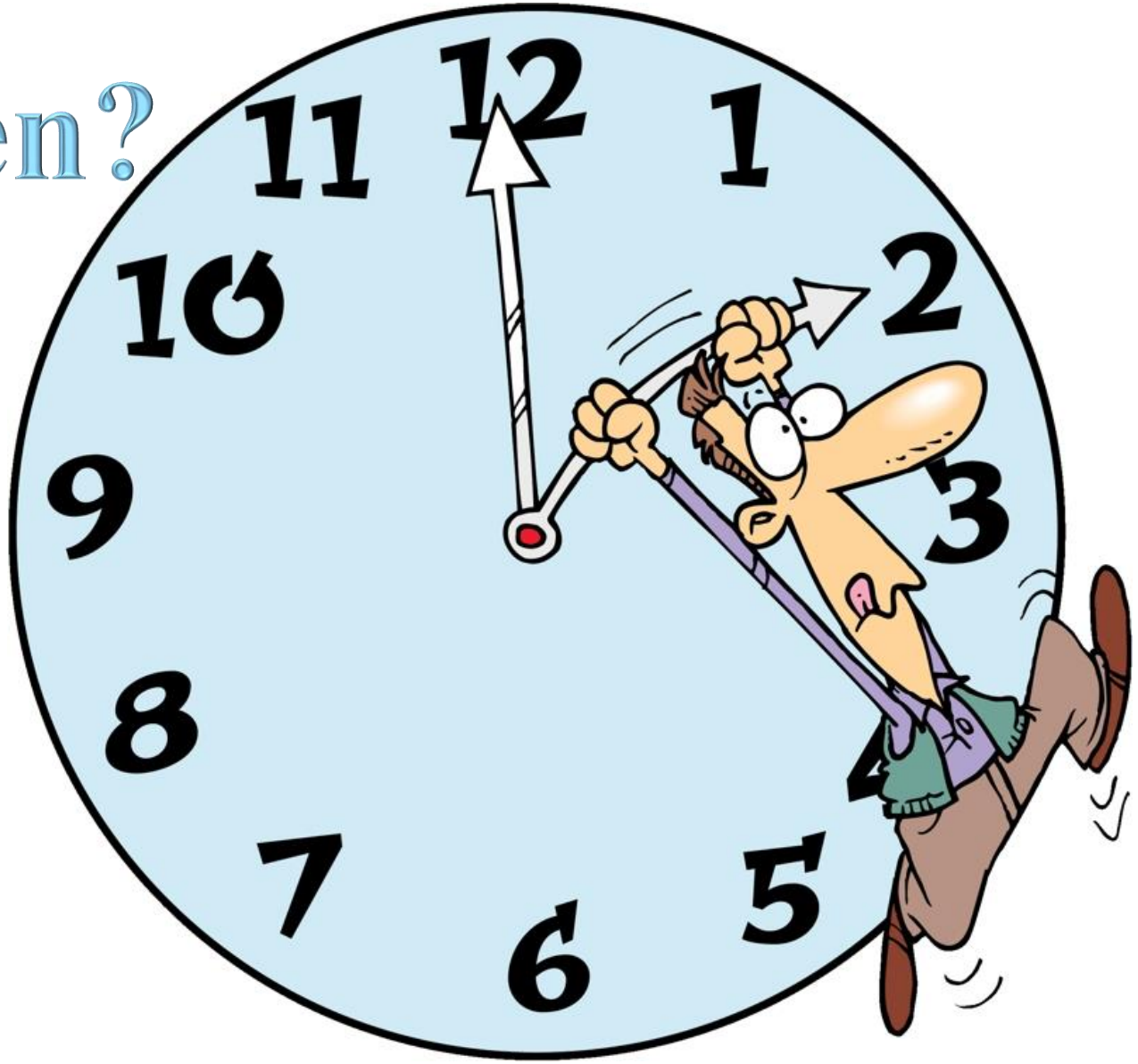
8.2.2: The organization shall document procedures for timely complaint handling in accordance with applicable regulatory requirements. These procedures shall include at a minimum requirements and responsibilities for investigating complaints.

8.3: The evaluation of a nonconformity shall include a determination of the need for an investigation and notification of any external party responsible for the nonconformity.

So…Why Do We Investigate?

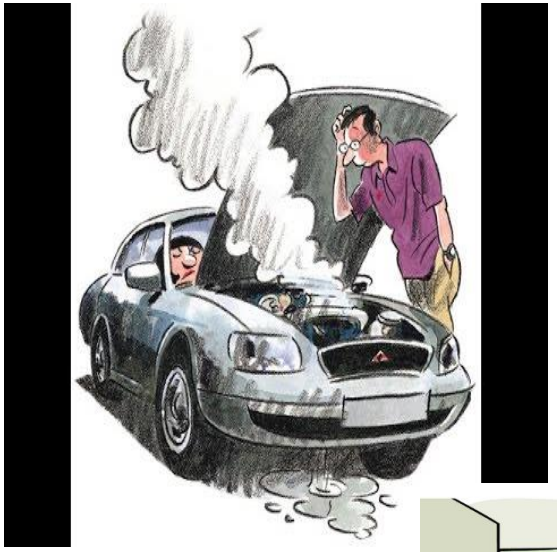
- Compliance to regulations
- Maintain patient safety
- Customer satisfaction
- Process improvement
- Makes good business sense

When?



When Do We Do Investigations?

- When failures occur:
  - Products,
  - Raw Materials,
  - Components,
  - Processes (including IT),
  - Audit observations, etc.



- When we receive a complaint.

- When an Adverse Trend is observed:
  - Environmental monitoring,
  - Product results moving toward failure,
  - Multiple simple errors identified, etc.

How Do We Investigate?

"We can't solve problems by using the same kind of thinking we used when we created them"

Albert Einstein

How? General Considerations

- One size doesn't fit all.
- Simple errors require simple documentation.
- More serious deviations require broader investigations.
- Use your risk evaluation process to determine risk.
  - Low risk items:
    - Smaller problem solving team,
    - Use of simpler tools (brainstorming, fishbone, 5 whys).
  - Higher risk items:
    - Larger problem solving team
    - Use more sophisticated tools (screening experiments, Design of Experiments (DOE), fractional factorial experiment and full factorial experiments)

How? General Considerations (cont.)

- Best tool: inquisitiveness – how far could this extend?
- Wide perspective: Try to relate, not separate, similar issues.
- Human error: rarely a sufficient root cause.
- Always verify, never assume.
- Start: As soon as you are aware of the problem.
- Keep on a schedule.
- Communicate progress to management.
- Escalate when necessary.

How? Define the Team

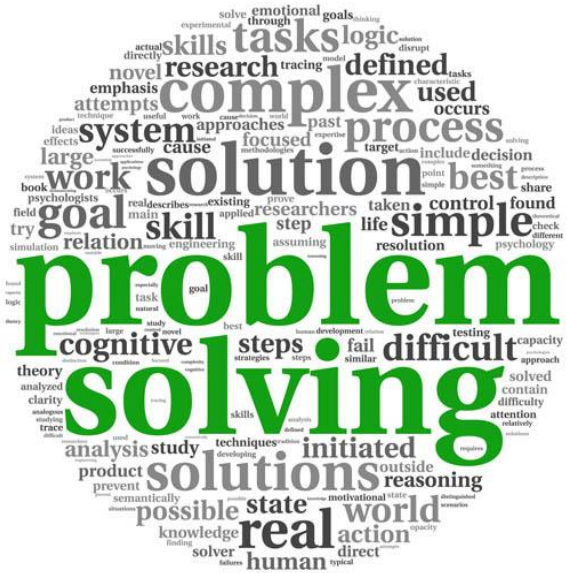
- Identify an Owner
- Identify Team Members:
  - Management Sponsor
  - Trained Problem Solver (Green Belt, Black Belt)
  - Quality Assurance/Quality Control
  - Operations/Manufacturing
  - Technology (including IT)
  - Engineering
  - Regulatory
  - Other

How? Define the Problem

- Problem: Undesired result from expected outcome.
  - Any defect, error, deviation, complaint, etc.
- Based on fact.
- Clearly define issue.
- Determine in scope/out of scope.

How? Define the Problem (cont.)

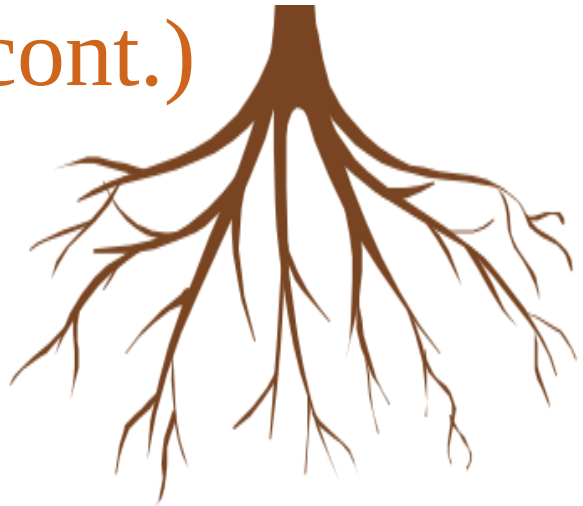
- Answer the questions (4Ws, 2Hs, 1C)
  - Who was involved?
  - What happened?
  - When did it happen?
  - Where did it happen?
  - How much information/product was involved?
  - How often has it happened in the past?
  - Consequences?



How? Getting to Root Cause

- Getting to Root Cause:
  - –Write an investigation plan:
    - Determine areas to be investigated
    - Determine what data needs to be collected
    - Describe investigation activities and tools
    - Assign responsibilities
    - Establish timeframe for completion
  - –Back up conclusions with facts/data

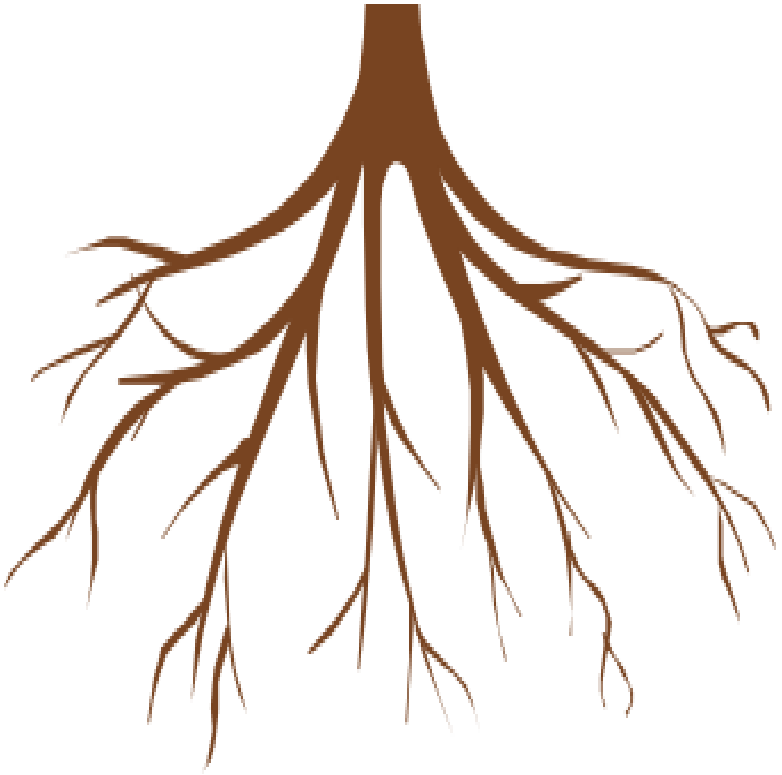
How? Getting to Root Cause (cont.)



- Helpful Hints:
  - Assume you caused the problem
  - Assume supplier caused the problem
  - Use Root Cause analysis tools (as needed, required)
  - There may be more than one cause
  - In some cases –
    - root cause may not be apparent
    - probable root cause may be only option

How? Getting to Root Cause (cont.)

- Each investigation must address the following elements:
  - Historical Evaluation
  - Process/Methods
  - Materials Used
  - Equipment/Instrument
  - Personnel
  - Laboratory Analysis
  - Validation



Historical Evaluation

- Potential Questions:
  - Have we seen this before on this product?
  - Have we seen this with other products?
  - Have we seen this before in this line?
  - Have we seen this before with these operators?
  - Have we seen this before with this supplier?

Processes/Methods Evaluation

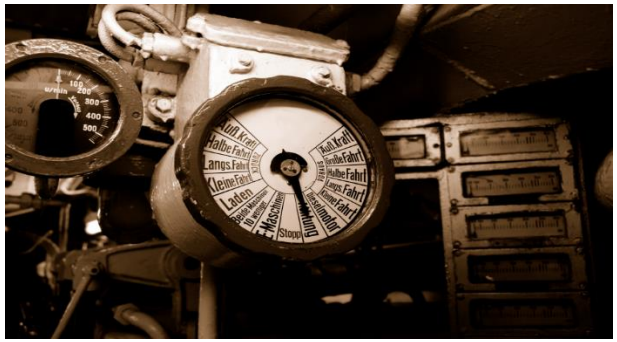
- Potential Questions:
  - Did we follow all instructions (MBRs and SOPs) as required?
  - Is this a new process or have there been process changes?
  - Has the supplier made any process changes?
  - Have we had failures with this process before?

Materials Used Evaluation

- Potential Questions:
  - Did we/suppliers use the correct item numbers?
  - Were materials properly released?
  - Were the materials handled and stored properly by us?
  - Were the materials handled/stored properly by the supplier?

Equipment/Instrument Evaluation

- Potential Questions:
  - Were instruments calibrated and maintained per SOPs?
  - Was equipment being operated within qualified limits?
  - Was any maintenance conducted on equipment prior to incident?



Personnel Evaluation

- Potential Questions:
  - Were personnel up to date on training?
  - Were new personnel involved?
  - Were personnel distracted during operations?

Laboratory Evaluation

- Were appropriate methods used?
- Were standards appropriate and qualified?
- Was equipment qualified and calibrated?

Validation Evaluation

- Was process operating within validated limits?
- Was this a new or recently revised process?
- Has the incident been described in the development or tech transfer reports?

Investigation Tools

Root Cause Analysis Tools

- Simple
  - Brainstorming
  - 5Whys
  - Cause and Effect (fishbone diagram)
- Complex
  - Design of Experiments
  - Contradiction Matrix (TIPS)
  - Fault Tree Analysis
  - Probability Risk Assessment

Tools – Brainstorming

- Produces many ideas/solutions in a short time.
- Covers all ideas within a group regardless of team member:
  - Titles.
  - Roles.
  - Personalities.
- Leverages total team involvement.
- Facilitates creative thinking.
- Separates idea generation from idea judging.

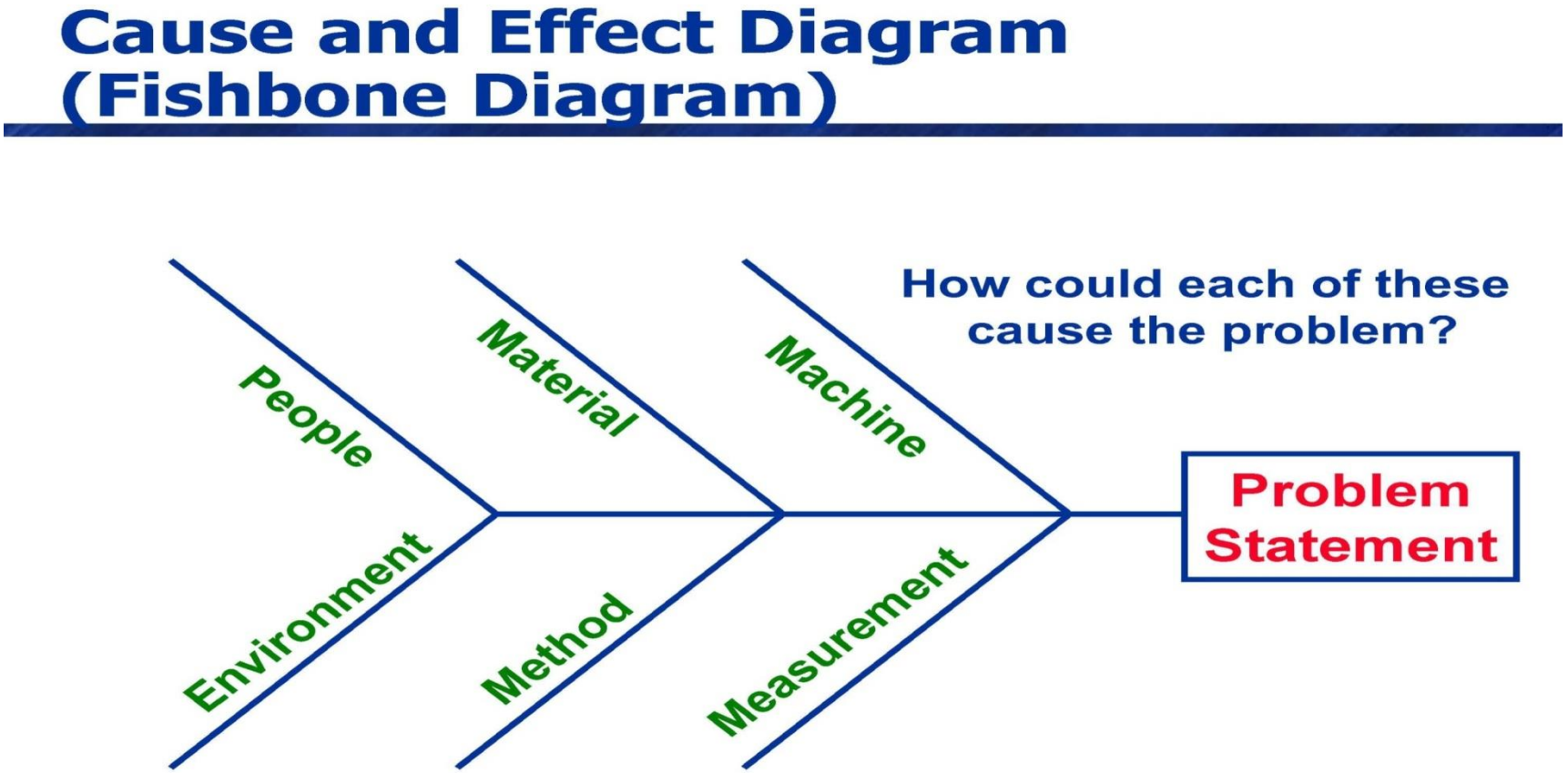
Brainstorming - Dos and Don'ts

- Do write down every idea, regardless of how unlikely it is.
- Do have an open session: Encourage participants to continue to write down additional ideas as they listen to others' ideas. People shall not censor themselves!
- Do not allow discussion of ideas until session is complete. It is okay to ask questions for clarification, but not to challenge other peoples' ideas.
- Do not terminate discussion before everyone is out of ideas.
- Do document your results

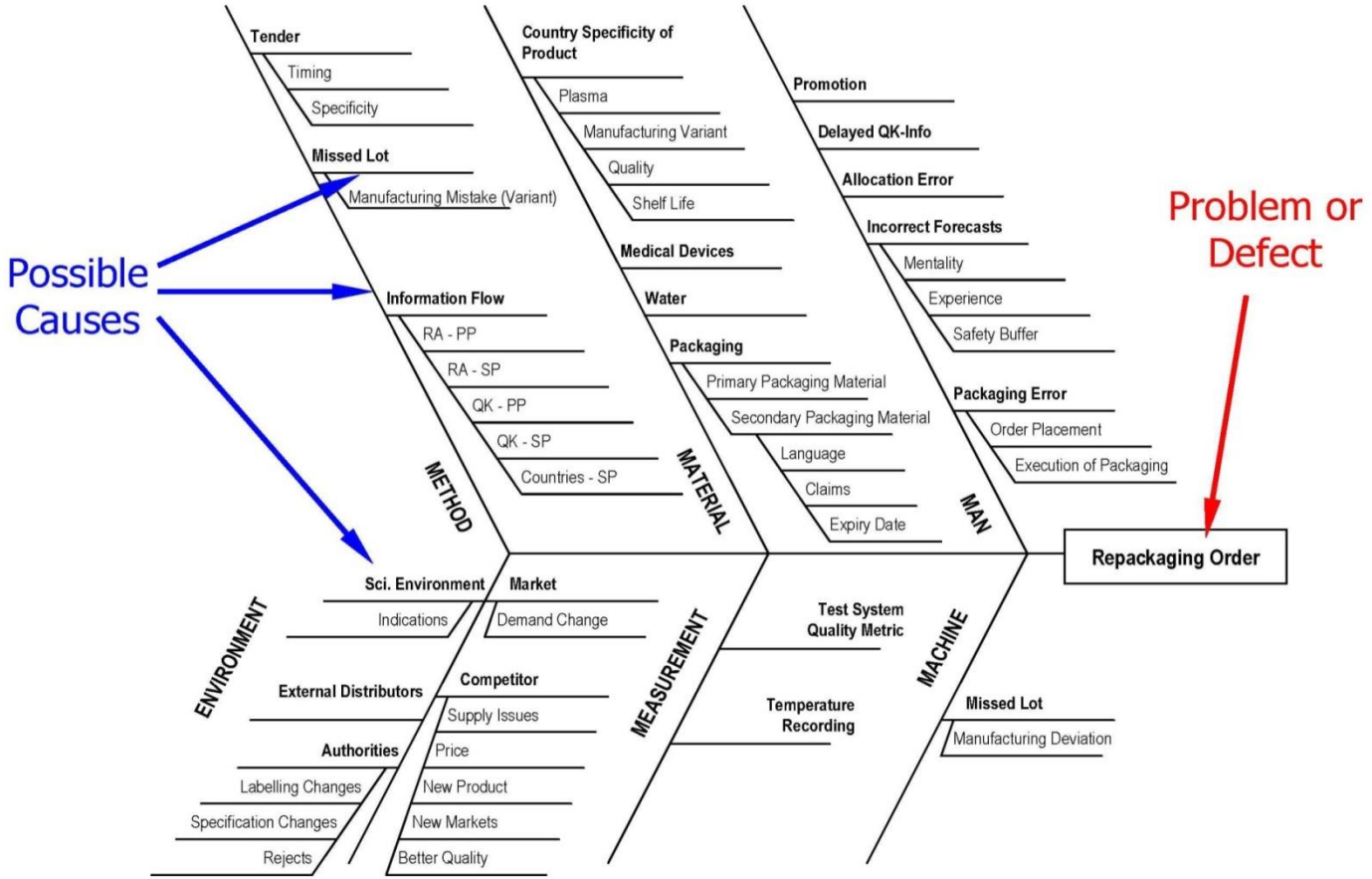
Tools – Cause & Affect Diagram (Fishbone)

- Ensures balanced list of ideas generated.
- Acts as discussion guide.
- Assists in determining root causes.
- Sorts & relates the factors that may affect a process when little quantifiable data is available.
- Determines cause of problem vs. symptom.
- Graphically displays level of process understanding.

Fishbone Diagram



Cause & Effect Diagram - Example



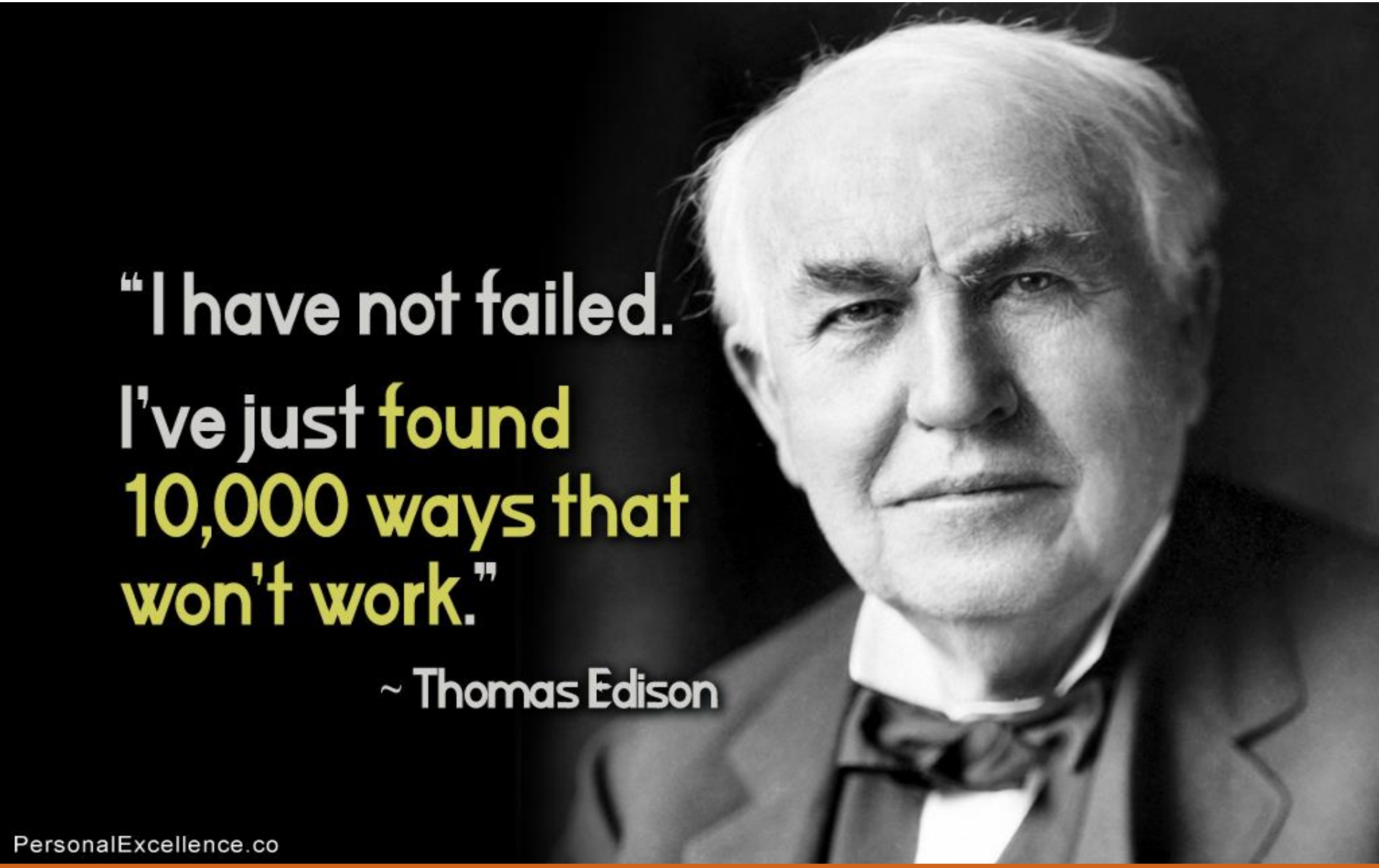
Tools – Five Whys

- Simplest of tools.
- Helps identify root cause..
- Easy to complete.
- Peels away layers of symptoms.

Tools – Five Whys (cont.)

The end result is that the final “Why” leads the team to a statement (root cause) that the team can take action upon.

Common Mistakes



Common Mistakes (cont.)

- Allocating blame.
- Assuming the cause is always the same.
- Rushing to judgment.
- Patching vs. fixing

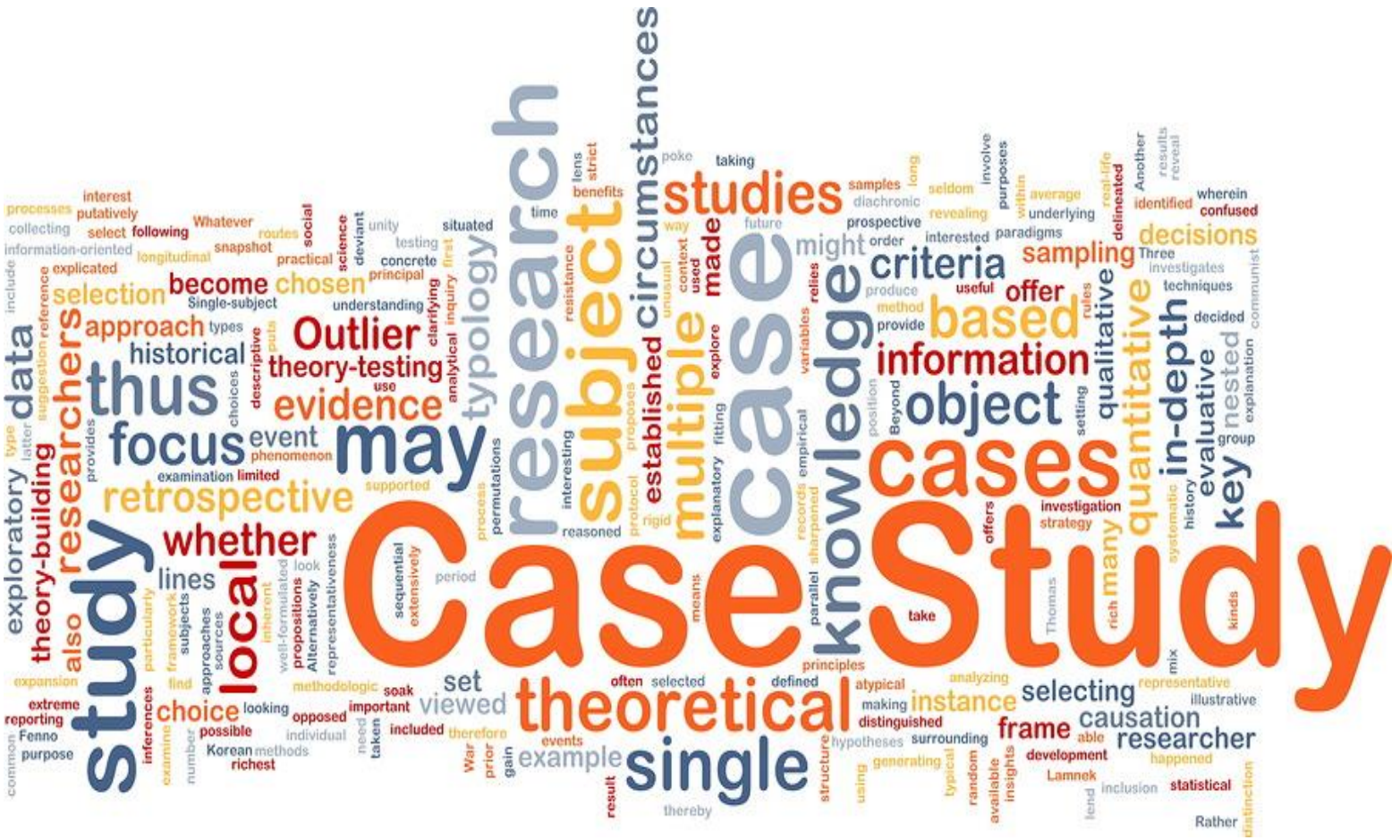
- Lacking focus; disorganized approach
- Lacking problem solving process

Documenting Results

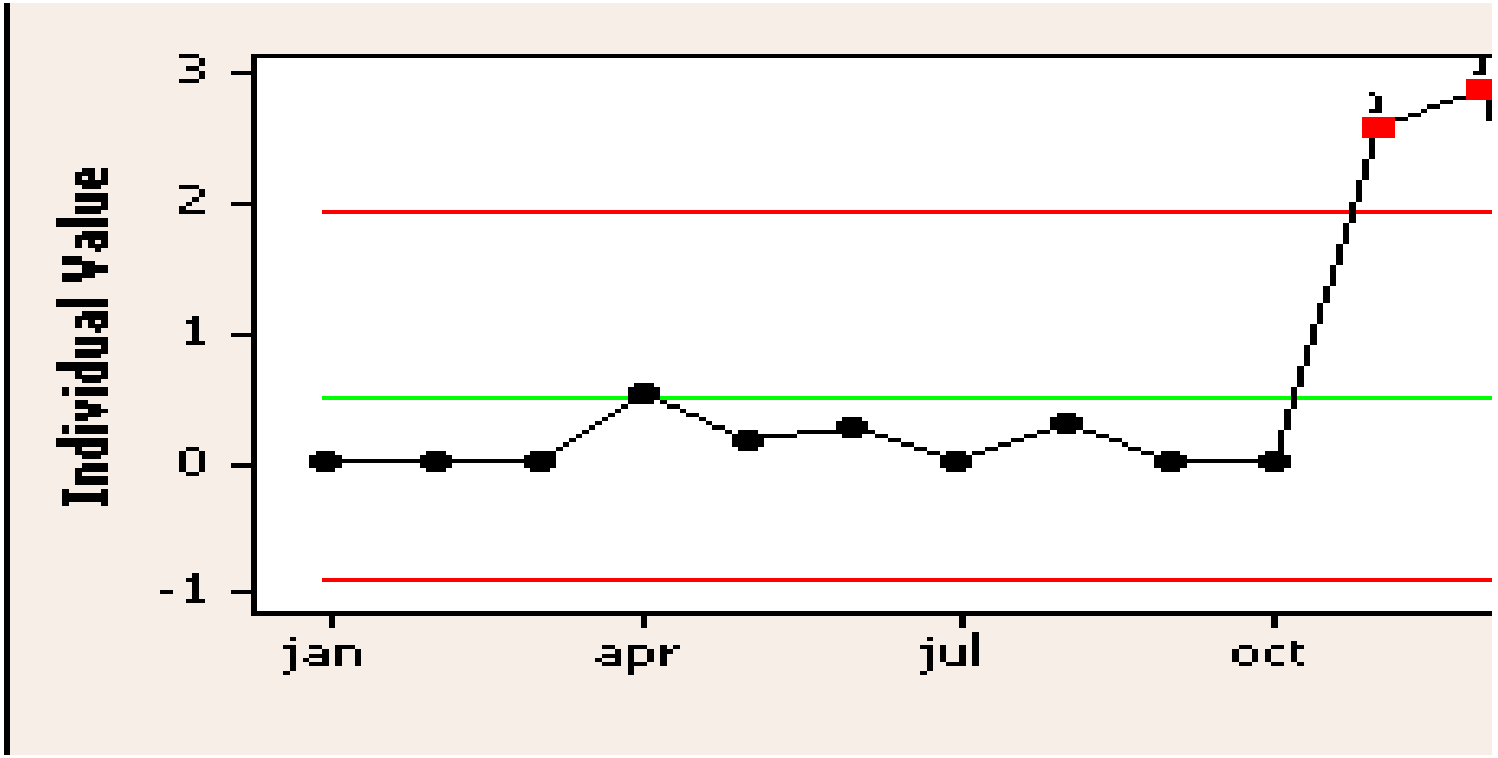
- Clear
- Concise
- Readable and understandable
- Use consistent terminology
- Explain acronyms
- List all references/attachments
- May create and use template

Documenting Results (cont.)

- Identify team members.
- State the problem being investigated.
- Identify the tool(s) used.
- Identify the results from the tool(s).
- State the root cause for the failure.



How Do We Investigate
Device Example



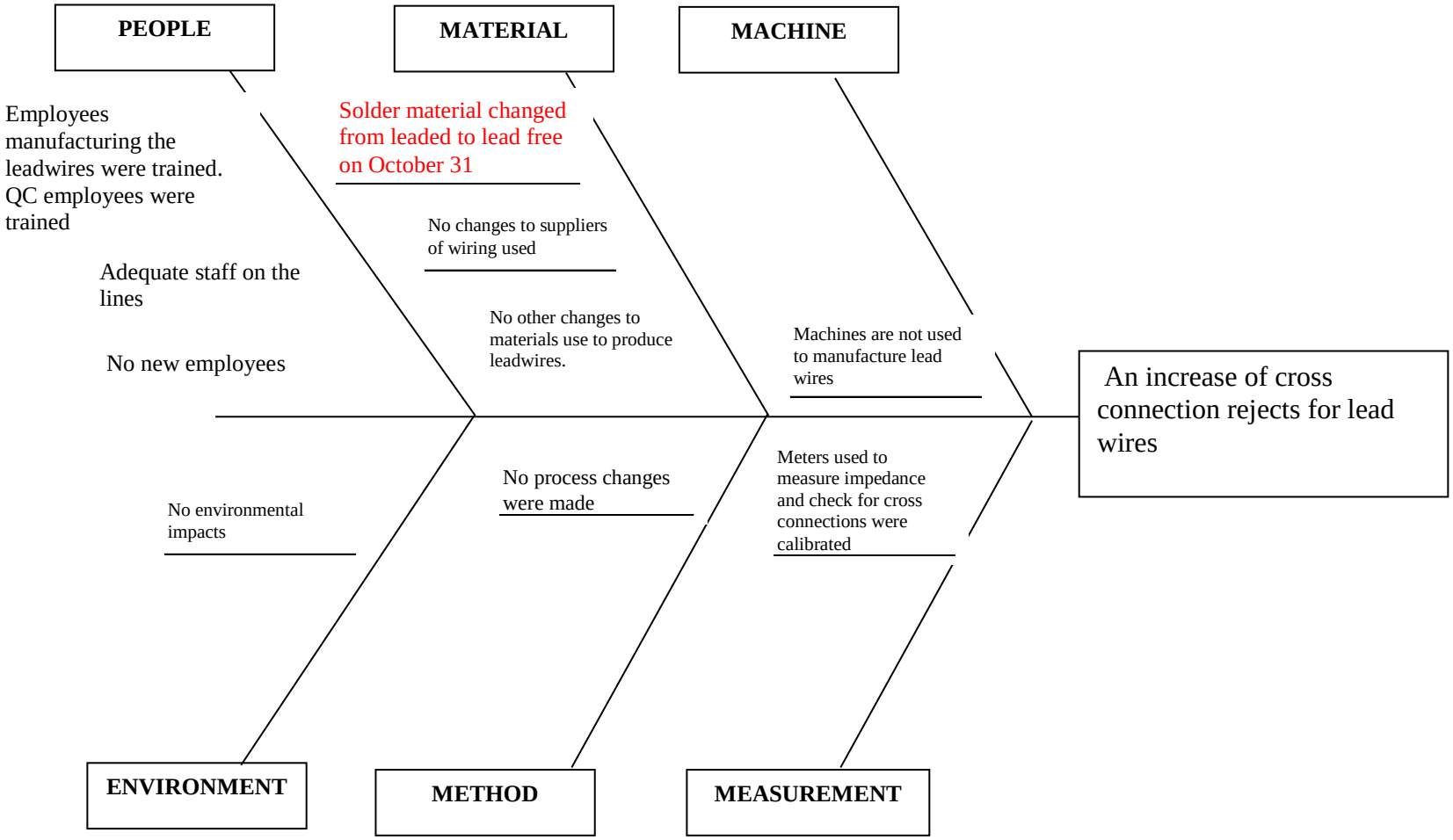
How Do We Investigate Device Example

- Gather the team
  - Manufacturing
  - Quality
  - Purchasing
  - Engineering
- Define the Problem
  - On December 1, **(When),** the Quality Supervisor **(Who)** saw an increased number of cross connection failures **(What)** over the last month **(How Long)** for lead wires manufactured in the lead wire production area **(Where).** These failures have caused a 25% decrease **(How much)** in production yield **(Consequence).**

How Do We Investigate
Device Example

- Investigation Plan
  - –The team used a fishbone diagram to look at
    - Man
    - Materials
    - Method
    - Manufacturing
    - Measurement, and
    - Mother Nature

How Do We Investigate Device Example



How Do We Investigate
Device Example

- 5 Whys
  - Would lead free solder cause cross connections
    - Incomplete soldering
  - Why incomplete soldering
    - Lead free solder used incorrectly
  - Why lead free solder used incorrectly
    - Supervisors not aware that larger tips needed to be used
  - Why supervisors not aware
    - The change to lead free solder was not validated prior to using it in production

How Do We Investigate
Device Example

- Root Cause
  - » Change made in the type of soldering material used without validating its impact to the manufacturing process and proper validation.

Investigations Summary

- Required by law.
- Supports patient safety.
- Makes good business sense.
- Include the right people.
- Clearly identify the problem.
- Set realistic deadlines.
- Drive to root cause(s).
- Document the results
- Remember your audience.
- THINK !!!!

Questions?

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