

Deviation Management

DCVMN regional Workshop Sao Paulo,
November 24-28th

Dr. Sandra Olga Rumiano

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Agenda

- Worldwide Regulatory Requirements
- Deviations / Incidents / Observations / OOS (out of specifications) / OOT (out of trends) / OOE (out of expectations) / complaints – what can go wrong in vaccines supply chain and how to manage it?
- Root Cause Analyses tools.
- Corrective Actions vs CAPA Plan.
- Root Cause Analyses : practical exercises:
- Questions open session.
- Attendants Evaluation.

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Worldwide Regulatory Requirements

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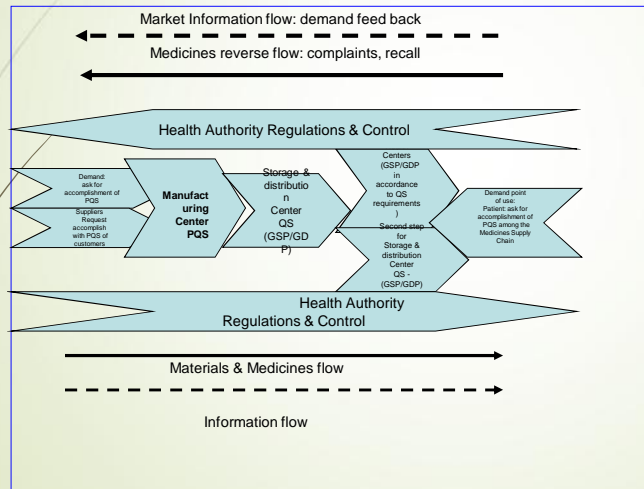
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ICH Q10 Pharmaceutical Quality System



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PQMS : Medicines supply chain management (MSCM) and Pharmaceutical Quality System



As a result Supply chain connects Pharmaceutical Quality Systems With QS that Includes suppliers, Third parties centers, storage and distribution centers.

An integrated PQS through the Medicines Supply Chain guarantee that medicines are Supplied in accordance to established quality guidelines to prevent complaints, recalls, returned or salvaged products, and defective products entering/circulating in the Market.

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All non conformities in process, quality, specifications, efficacy of medicines

- Should be reported
- Should be investigated
- Corrections should be applied
- CAPA Plans:
 - Should be established
 - Reported
 - Follow up

Deviations / Incidents / Observations / OOS
(out of specifications) / OOT (out of trends) /
OOE (out of expectations) / complaints – what
can go wrong in vaccines supply chain and
how to manage it?

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Deviations

- Deviation: Failure to comply with all rules and procedures processes under a Pharmaceutical Quality Management System.
- Pre - Scheduled Deviation : the modification of the processes and requirements of Quality Management System prior to its execution.

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Incidents / Observations

- An incident is an unplanned or undesired event that adversely affects a company's work operations. Incidents include work-related injuries, occupational illnesses, property damage, spills, fires or near miss events that could have resulted in any of these.
- Event: a definite and separate occurrence
- Observation:
 - note taken during a process where it doesn't meet expectations and ask for clarification.
 - act or instance of noticing or perceiving

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AEFIs: Adverse effects following immunization

<p><input checked="" type="checkbox"/> Checklist</p> <p>A. Background</p> <ul style="list-style-type: none"> <input type="checkbox"/> Review the product information for the vaccine, including the vaccine's history, composition, and manufacturing process. <input type="checkbox"/> Review the vaccine's safety data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's efficacy data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's quality data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's regulatory status, including the results of clinical trials and post-marketing surveillance. <p>B. Vaccine and process history at organizational level</p> <ul style="list-style-type: none"> <input type="checkbox"/> Review the vaccine's history, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's safety data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's efficacy data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's quality data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's regulatory status, including the results of clinical trials and post-marketing surveillance. <p>C. Clinical data and quality assurance</p> <ul style="list-style-type: none"> <input type="checkbox"/> Review the vaccine's safety data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's efficacy data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's quality data, including the results of clinical trials and post-marketing surveillance. <input type="checkbox"/> Review the vaccine's regulatory status, including the results of clinical trials and post-marketing surveillance. <p>D. 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OOS (out of specifications) / OOT (out of trends) / OOE (out of expectations)

- Out-of-Specification (OOS) Results :A result that falls outside established acceptance criteria which have been established in official compendia and/or by company documentation.
- Out-of-Expectation (OOE) Results: 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.
- Out of Trend (OOT) Results: A time dependent result which falls outside a prediction interval or fails a statistical process control criterion.
 - A trend is a sequence of temporal procedures, e.g. for the manufacture of different batches of a product. There are two types of trends:
 - In one case, no trend is expected, e.g. in production or when analyzing process data where everyone expects that they are under statistical control.
 - In the other case, a trend is expected. One typical example for that is stability testing where one expects that the content of the API reduces over the storage period, or that the quantity of impurities increases over time.

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Complaints

Complaint means any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness of a medicine or a medical device after it is released for distribution.

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Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

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Companies should have an investigation process to ensure that:

- All unplanned and or communicated non conformities as general concept are investigated
- Root cause is identified
- Actions are taken:
 - Contingent or correction action: action or measure taken to eliminate or correct a detected nonconformity.
 - Corrective action means action to eliminate the cause of a detected nonconformity or other undesirable situation.
 - Preventive action: Action taken to eliminate the cause of a potential nonconformity or other undesirable situation.
- Corrections and CAPA Plan has a established follow up cycle

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Root cause analysis tools

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- Brainstorming and Mind mapping as lateral thinking supporting tools
- W questions
- Fish bone:
 - Ishikawa
 - 6 M
- Fault tree analysis
- Gap analysis & Wish bone: to improve

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Brainstorming

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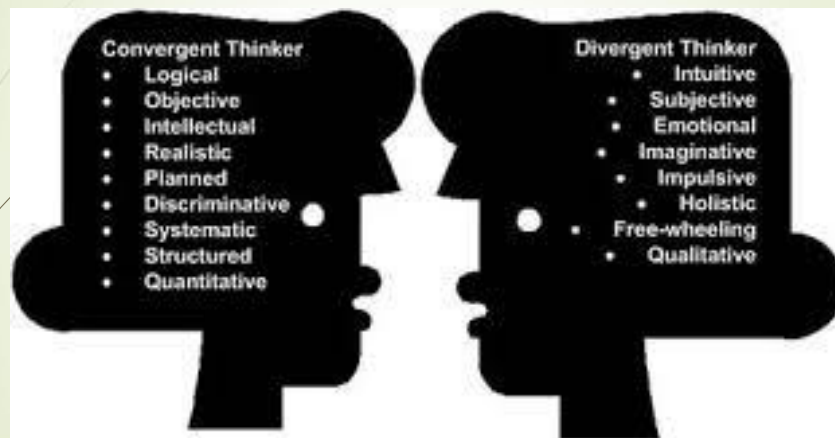
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Rules for Brainstorming

- ◆ Clearly state the objective of the session.
- ◆ Generate as many ideas as possible.
- ◆ Let your imagination soar.
- ◆ Do not allow criticism or debate.
- ◆ Combine ideas.

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Six thinking hats

What are my powers when wearing each hat?



Asking questions:

- What do we know?
- What do we need to know?
- How do we get this information?



Expressing emotion:

- What are my gut feelings?



Judging:

- What are the difficulties & weaknesses?



Being optimistic:

- What are the strengths & opportunities?



Being creative:

- New ideas?
- New opportunities?
- How can it be improved?



Thinking about thinking:

- What's been learned?
- What's next?

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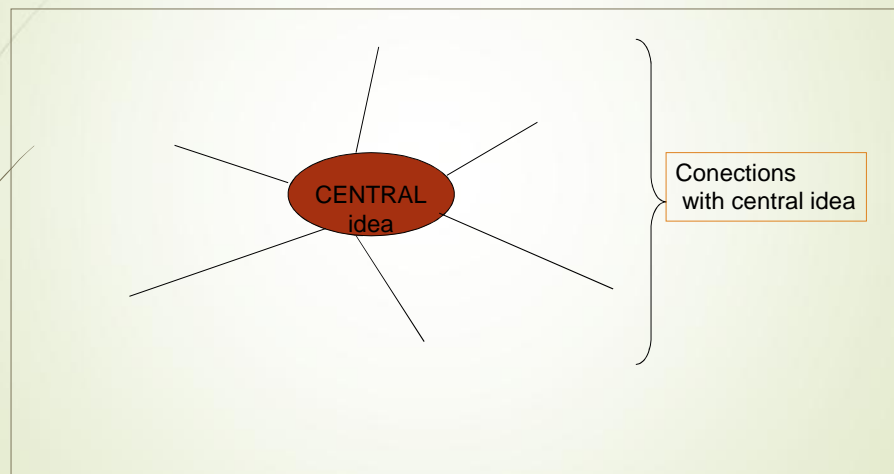
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Mind mapping

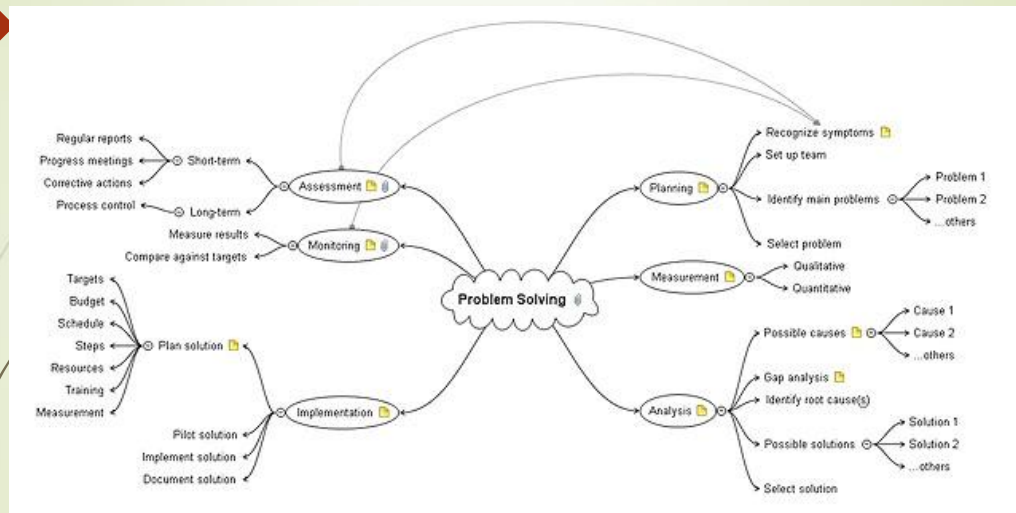
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mind mapping



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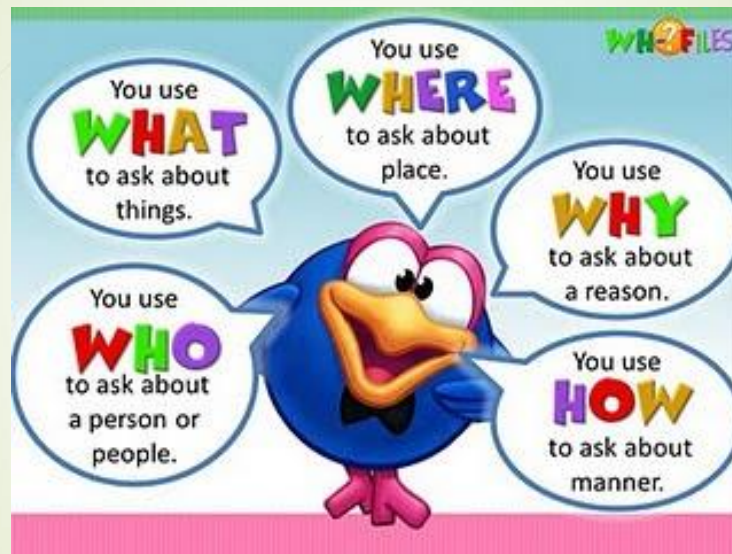
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W questions

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W questions and how to applied them

where when
 who **why**
 what
 which how

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Fish bone: Ishikawa

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Kaoru Ishikawa (1915 - 1989)

La frase del día...!

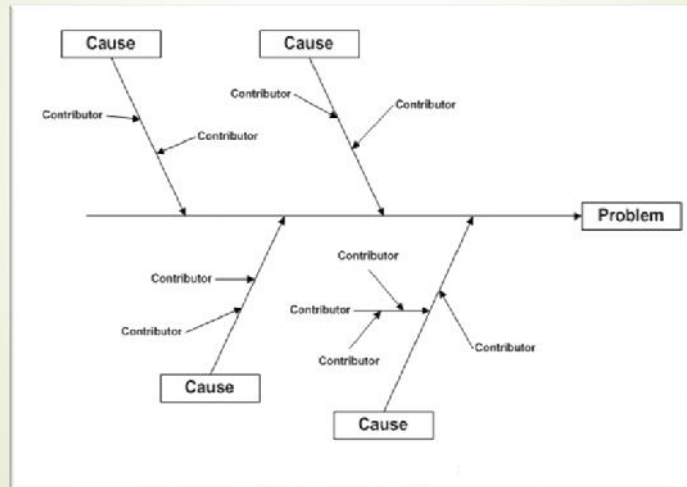
Ninguna empresa puede ser mejor o peor que las personas que la integran.

A company is neither better nor worse than people who work there within.

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Classic style



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- Each cause or reason for imperfection is a source of variation. Causes are usually grouped into major categories to identify these sources of variation. The categories typically include:
 - People: Anyone involved with the process
 - Methods: How the process is performed and the specific requirements for doing it, such as policies, procedures, rules, regulations and laws
 - Machines: Any equipment, computers, tools, etc. Required to accomplish the job
 - Materials: Raw materials, parts, pens, paper, etc. Used to produce the final product
 - Measurements: Data generated from the process that are used to evaluate its quality
 - Environment: The conditions, such as location, time, temperature, and culture in which the process operates

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The 6 Ms (used in manufacturing industry) from Toyota

Machine (technology)

Method (process)

Material (Includes Raw Material, Consumables and Information.)

Man Power (physical work)/Mind Power (brain work)

Measurement (Inspection)

Milieu/Mother Nature (Environment)

That includes two other causes non worldwide applied:

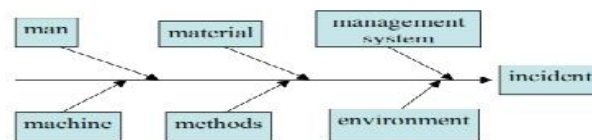
Management/Money Power

Maintenance

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Basic elements of root cause:



Some examples of each of these root cause elements are as follows:

Materials	Machine/Equipment
<ul style="list-style-type: none"> - Defective raw material(s) - Wrong type of material for job - Not enough raw material 	<ul style="list-style-type: none"> - Incorrect selection of tool or equipment - Poor equipment maintenance or design - Poor equipment or tool placement - Defective equipment or tool
Environment	Man
<ul style="list-style-type: none"> - Orderly workplace - Job design or layout of work - Surfaces poorly maintained - Physical demands of the task - Other conditions (noise, lighting, etc.) 	<ul style="list-style-type: none"> - No or poor management involvement - Inattention to task - Task hazards not guarded properly - Other (horseplay, inattention, etc.) - Stress demands
Methods	Management System
<ul style="list-style-type: none"> - No or poor procedures - Practice does not mesh with written procedures - Poor communication 	<ul style="list-style-type: none"> - Training or education lacking - Poor employee involvement - Poor recognition of hazard - Previously identified hazards were not eliminated

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The 7 Ps (used in marketing industry): check used in complaints!!!!

Product/Service

Price

Place

Promotion

People/personnel

Positioning

Packaging's

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The 5 Ss (used in service industry): **what about suppliers and GSP/GDP??**

Surroundings

Suppliers primary vs secondary

Systems

Skills

Safety

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Root Cause Analyses : practical exercises:

Deviation in vaccine filling: environmental results OOS after maintenance intervention

Machine cleaning : is done disorderly, some pieces of clothes are used for cleaning critical parts and protective doors, staff movement is fast because a new lot should be filled.

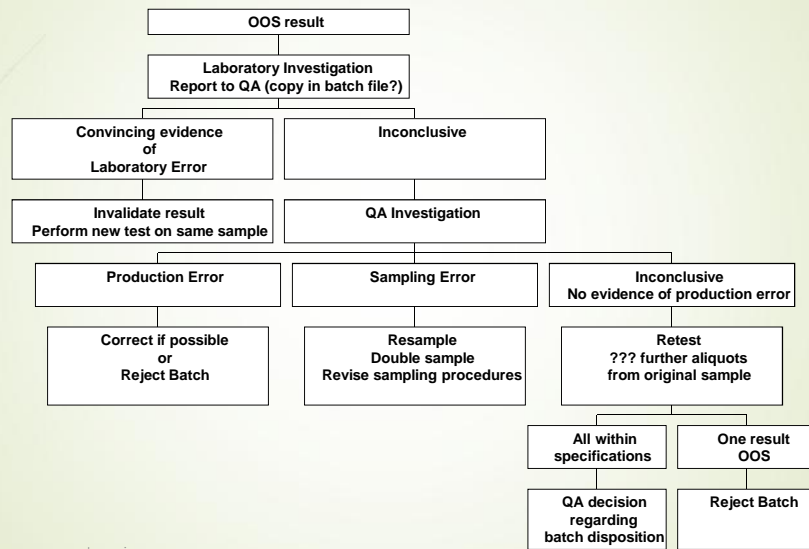
AEFI during CT document was found uncompleted during an internal audit process

BCG are sent to different countries, labels accomplish the regulatory requirements of each HA, when you are reviewing the BR you found 3 labels coming from 3 different lots, one of them is designated to Peru and the other two to Chile. The target Market is Chile.

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Fault tree analysis

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Some findings

OOS

- SOP for the reporting and investigation of Out of Specification (OOS) results not implemented
- No record of OOS results
- In case of an OOS, re-testing was done, however, the results were recorded on a loose piece of paper, other sheets were not appropriately completed e.g. method number, no of samples, LIMS number

Root Cause Analyses : practical exercises:

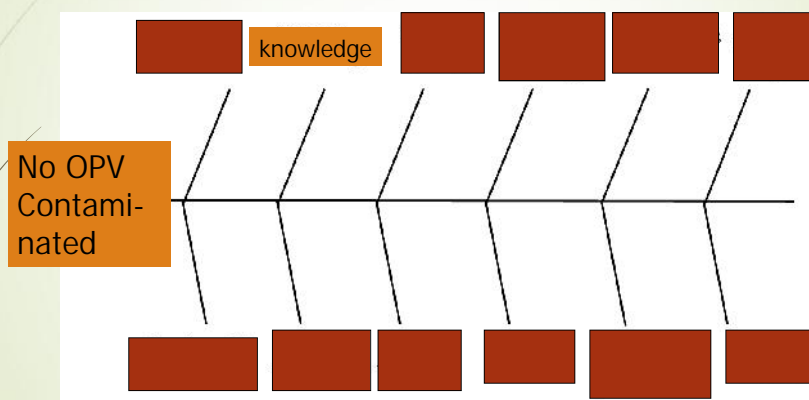
OOS found in WFI sampling in preparation elements area POU (microbiological count OOS) was found at the end of incubation period of samples, you formulated 2 lots of vaccines during the concern week

OOS found environmental monitoring where identification results indicates more than 10 <<ufc7wright hand in gloves of staff in charge of filling machine (grade A/B) and fungi's collected in settle plates grade B surrounding storage area for double packaging sterile grips and cleaning cloth as well as disinfectant devices. The filling is aseptic.

CT: OOS blood results were found in site number 2 of 6. You ask for an investigation

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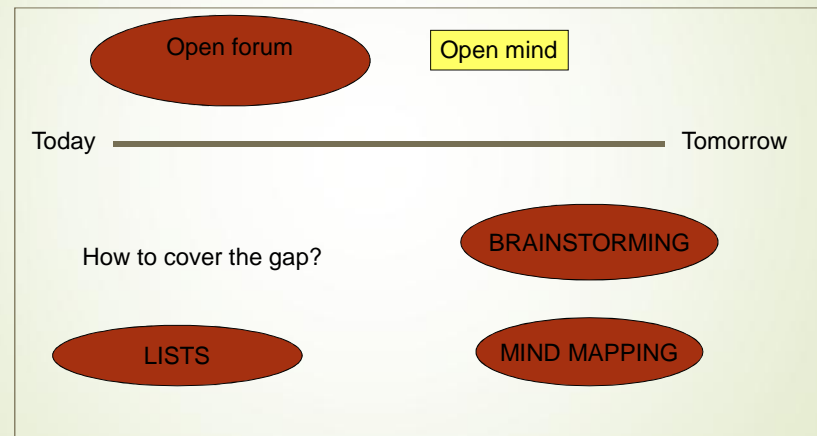
wish bone: Opportunities to be discover



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Gap analysis



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Quality System Fundamentals and main documents

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Key steps in Pharmaceutical Quality System

1. Implementation based on risk assessment and knowledge management
2. Maintenance: Status of Control:
 1. CAPA follow up
 2. KPIs
3. Improvement: PDCA cycle



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What is CAPA in accordance to ICH Q 10 and Q9?

- Today the majority of CAPAs start with exceptions and are “Manufacturing Focused”— Deviations, Non-Conformances, Annual Product Review, Management Review, Complaints, Risk Management, Validation, etc
- Patient focused
- Risk based Effort, resources and timelines Proportional to patient risk.
- Management and Responsible Management Review

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Root Cause Analyses : practical exercises:

Vaccines Supply chain complaint: broken vials in OPV (transport from Mexico to Paraguay, via Panama, air cargo)

Flu Vaccines Supply chain complaint: broken ampoules found (transport from Iran to Argentina, via Panama, air cargo)

BCG ampoules: cake was found different than usual

Record on Enviroteiner for yellow fever vaccine failure during air transport from Brazil to Argentina. Internal data loggers function properly. The local responsible claim.

One year after a CT is finished your Company receives a complaint of a the family of a subject that argue is suffering from the consequences of the immunization received.

Final discussion

Why and where we fault?

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Questions: open session.

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Thank you!

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