CBE
Centre for Biopharmaceutical Excellence

ICH Q10
Pharmaceutical Quality System (PQS)

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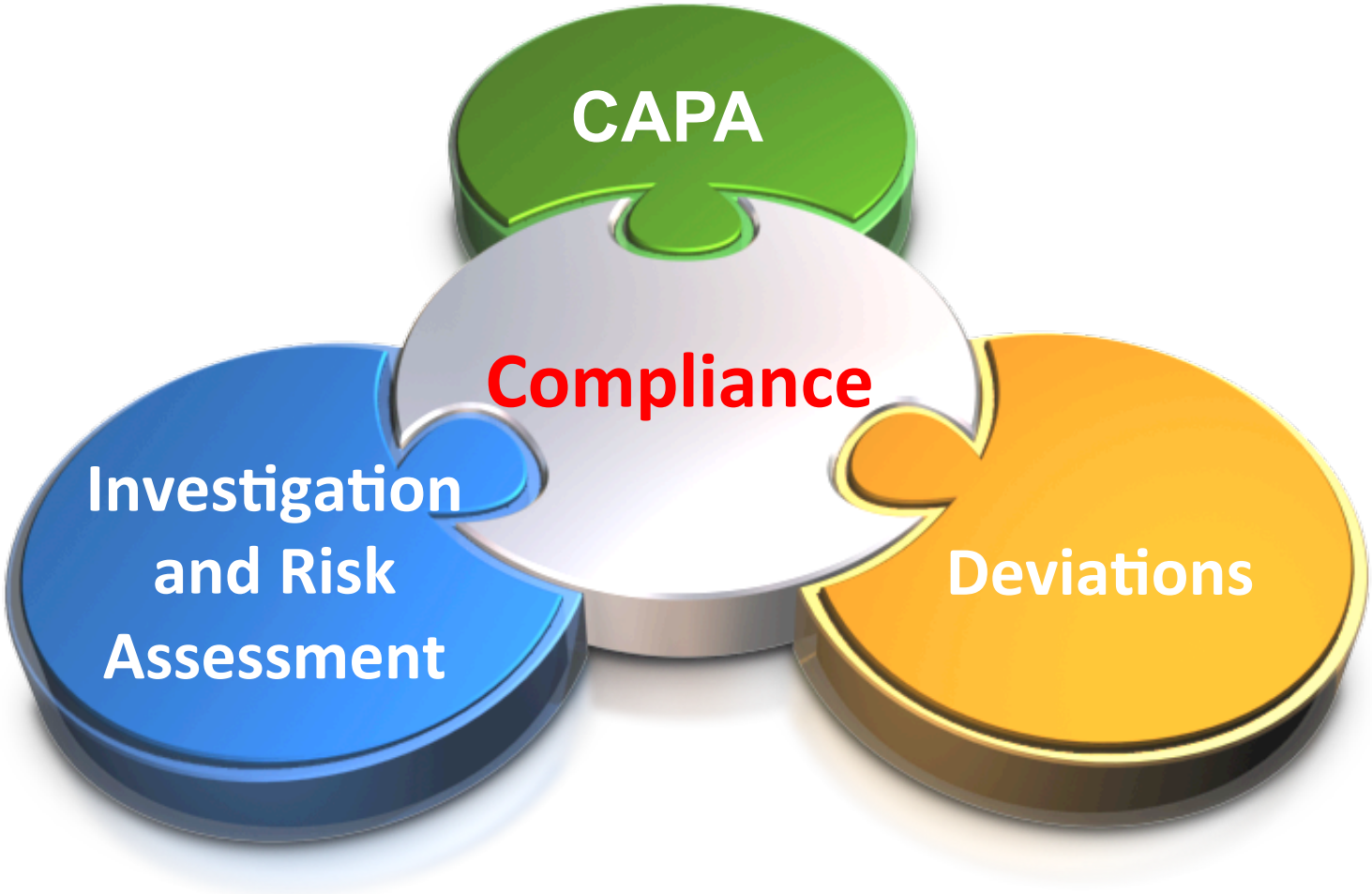
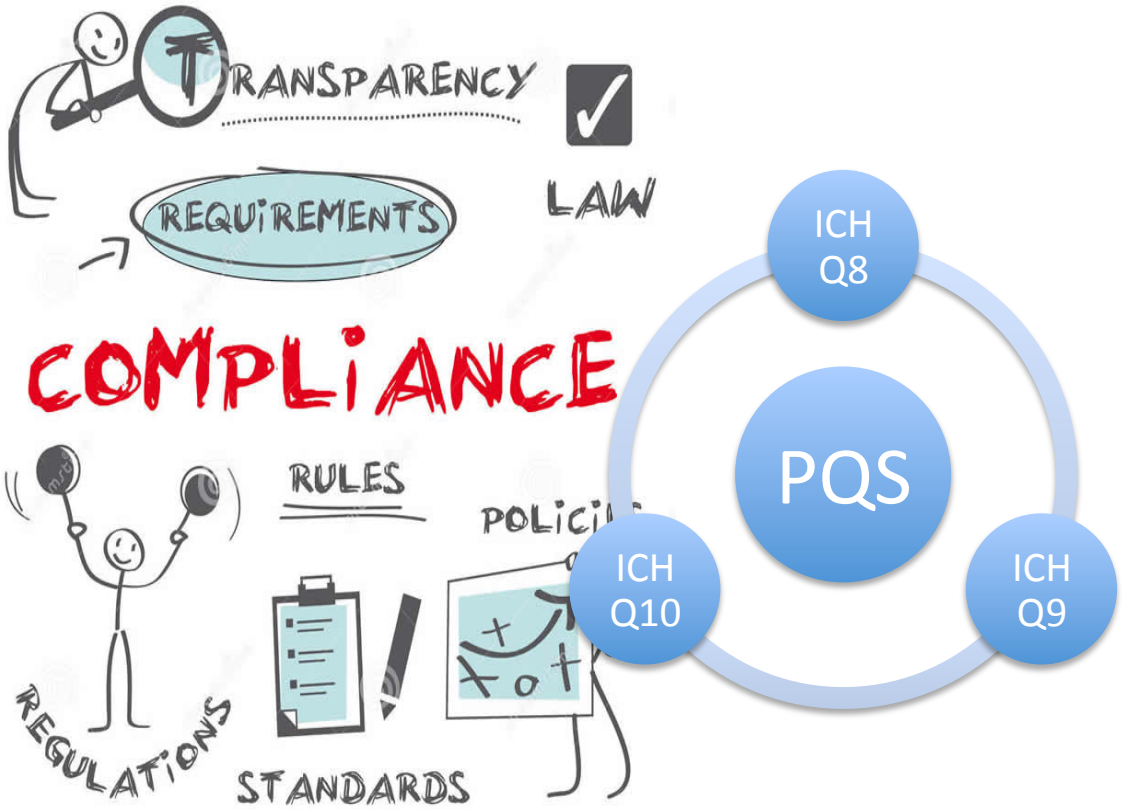
Deviations, Investigations and CAPA



Increasing Industry Complexity



Top Critical/Major Defect Areas

Most Frequent Defect Categories Observed		
Rank	Defect Category	Percentage of Critical / Major Deficiencies with this Defect Category
1	Investigation of anomalies	6.5%
2	Quality management	5.5%
3	Investigation of anomalies – CAPA	4.7%
=4	Contamination, chemical/physical (or potential for)	3.7%
=4	Supplier and contractor audit	3.7%
6	Quality management – change control	3.6%
7	Documentation - procedures/PSF/TAs	2.7%
7	Personnel issues – training	2.7%
=9	Design and maintenance of equipment	2.6%
=9	Documentation – manufacturing	2.6%
=9	Finished product testing - chemical	2.6%

The Defect Categories presented above account for 40.9% of all Critical / Major Deficiencies raised in 2013.

Manufacturers' Obligations

- **Oversight:** If a deviation occur, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate;
- **Release:** Deviations should be resolved before release
- **Stability:** Significant batch deviations may invoke a stability trial
- **PQR:** A review of all significant deviations, their related investigations, and the effectiveness of resultant CAPA taken.

PICs cGMP Expectations

- Any significant deviations are fully recorded and investigated; (GMP 1.3 iv.)
- Product assessment ….. an assessment of deviations from specified procedures; (GMP 1.3 vi.)
- Notes on special problems including details, with signed authorisation for any deviation from the Manufacturing Formula, Processing Instructions and Packaging Instructions (GMP 4.17 (i.)/ GMP 4.18 (h)
- If a deviation occur, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate. (GMP 5.15)

PICs cGMP Expectations

- Any significant deviation from the expected yield should be recorded and investigated. (GMP 5.39)
- an on-going stability study should be conducted after any significant change or significant deviation to the process or package. (GMP 6.30)
- The Competent Authorities should be informed if a manufacturer is considering action following possibly faulty manufacture, product deterioration, detection of counterfeiting or any other serious quality problems with a product. (GMP 8.8)

Deviation System Key Elements

Scope of the Deviation System

Batch(es) specific

applies to significant deviations (**planned or unplanned**), from standard operating procedures, manufacturing and packaging instructions that may have an adverse effect on product quality or "SQuIPP" (Safety, Quality, Identity, Purity and Potency / Strength).

Not batch specific – a GMP related incident

applies to GMP related incidents, that are not batch specific, which may have occurred during the manufacturing or within a supporting process such as HVAC or water systems etc.

Deviation System does apply to

- Maintenance and calibration – relating to GMP equipment and services
- Confirmed Out of Specification (OOS) events
- Laboratory procedures and test methods
- Stability failures
- Environmental monitoring and other GMP service excursions from action limits
- Supply chain / raw materials integrity
- Concurrent process validations and cleaning validations
- Phase III clinical trials material manufacture

Deviation System does not apply to

- Audit observations
- Product complaints and adverse events
- Returns and recalls
- Prospective qualifications and validations (these are handled within the Validation Master Plan procedures)
- Clinical Trial materials - Phase I / II manufacture

Healthy Deviation Management Environment

- Staff feel able to raise a deviation without blame
- Deviations are expected – its how we manage them that counts
- Good communication and judgment around when to report, or not – seek advice
- Constructive use of investigation and risk assessment tools

Alert and Responsive to Events

Responsibility of QA

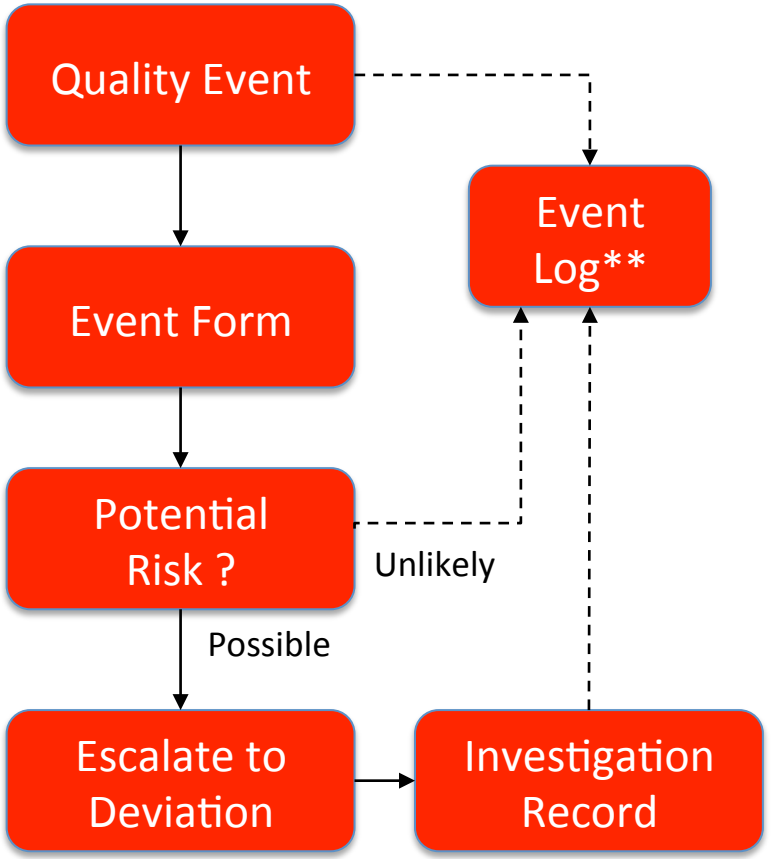
- Approval of planned deviations **before their implementation**;
- Classification of the deviation on the basis of Risk
- Overseeing a deviation investigation and review of any investigation / impact assessment report
- Filing completed deviation and incident reports.
- Deciding if a CAPA is required, or not
- Assessing subsequent corrective actions and investigation details
- Reviewing a deviation or incident report at point of release for use or for supply;
- Disposition of the product or material
- Updating and maintaining the Deviation/Event register

Deviation Decisions

- Should all Quality related “Events” be recorded ?
- Should all Events be referred to QA ?
- When does an event become a GMP deviation ?
- How is a “Significant” deviation defined ?
- Should all deviations be investigated ?
- How do we know its significant if its not investigated ?
- Should all investigations be documented / risk assessed ?
- Should CAPA be applied to all investigation outcomes

Filtration and Escalation Approach

- Start with a GMP related "Quality Event"
- Record on an Event Log
- Assess its potential significance
- Escalate to Deviation, or not
- Commence investigation



** Periodic and Annual Review

Categorise Event Categories for Trending

- Excursion from MBR
- Excursion from SOP
- Excursion from Test Method
- EM Excursion
- Equipment Breakdown
- Facility Breakdown
- Materials / Components
- Other

Example Only

Checklist to Prompt Preliminary Risk Decision (Potential Risk ?)

1	**Likely the event could impact SQuIPP ? (Safety, Quality, Identity, Purity, Potency)**	Yes No Unsure ?
2	Does the event result in an excursion from registered details for this product ?	Yes No Unsure ?
3	Likely the event could cause physical contamination or cross contamination ?	Yes No Unsure ?
4	Likely the event could cause loss of identity or traceability ?	Yes No Unsure ?
5	Likely the event could result in an out of specification result, if tested ?	Yes No Unsure ?
6	Likely the event could affect product quality or stability in the marketplace ?	Yes No Unsure ?
7	Is the event related to a GMP non-conformance or outside the “validated state” ?	Yes No Unsure ?
8	**Likely the event has compromised a CPP or a CQA ?**	Yes No Unsure ?

Recording and Evaluating Deviations

Most important to record the deviation quickly and accurately.

Record

- Date / time/ process step and stage of processing (pallet #)
- Batch #(s) and Item #(s)
- Equipment, process line and operator(s)
- Sequence of events causing the deviation
- How the deviation was identified
- What immediate action was taken (Containment)

Evaluation is very dependent on good records

- Line and product trend history
- Manufacturing batch records and line logs
- Level of in-process controls

Report Number:	QE/DR __ - ___	Title	

Refer to SOP 018030 when completing this form.	If this form is typed initial here to confirm version control has been checked:	

1. Quality Event Notice and Assessment ☐ Planned Deviation** ☐ Unplanned Deviation

Origin (√)	Description of the Event
☐ Excursion from MBR ☐ Excursion from SOP ☐ Excursion from Test Method ☐ EM Excursion ☐ Equipment Breakdown ☐ Facility Breakdown ☐ Materials / Components ☐ Other	(Batch # / Date / Process Line, Personnel etc.) or description of planned deviation and associated control actions.
☐ **Not Significant** ☐ **Potentially Significant (Progress to deviation)**	**Reasons for Conclusions:**

** Planned deviations require the prior approval of the QA Manager

Signed / Dated by QA Manager		

Record the event in the Quality Event Trend Register – If the event has been assessed as Not Significant record as QE or, if assessed as Potentially Significant then record as a Deviation (DEV) and continue with the completion of this form.

Report Number:	CAPA __ - ___	Title	

Refer to SOP 021 when completing this form.	If this form is typed initial here to confirm version control has been checked:	

This record combines (a) failure investigation (b) final risk assessment and (c) CAPA for any significant quality related event. It may be used stand alone or as a result of preliminary review of deviations, audits, complaints, vendor assessments or laboratory OOS.

Short Description of the Issue		Reference #: **

** Deviation #, Internal audit #, Complaint # or external audit # etc.

Origin (√)	
☐ Unplanned Batch Deviation ☐ Internal Audit Significant Observation ☐ External Audit Significant Observation ☐ Vendor Non-Conformance	☐ Planned Deviation ☐ Customer Complaint or Adverse Event ☐ Laboratory OOS ☐ Other:

If the event impacts product, write the product name, code and batch number here (or attach list):					
Product Name:		**Product Code:**		**Batch No:**	
QA Manager (sign)			**Date:**		

1. Investigation and Test Plans

Conduct a formal investigation of the issue. This investigation must be overseen by the QA Manager. Describe the overall investigation plan and any sampling and test/inspection plan.

Investigation Plan (describe the investigation actions required ie things that must be reviewed including any trends and records)	Testing / Inspection Plan (describe any sampling and test plan)

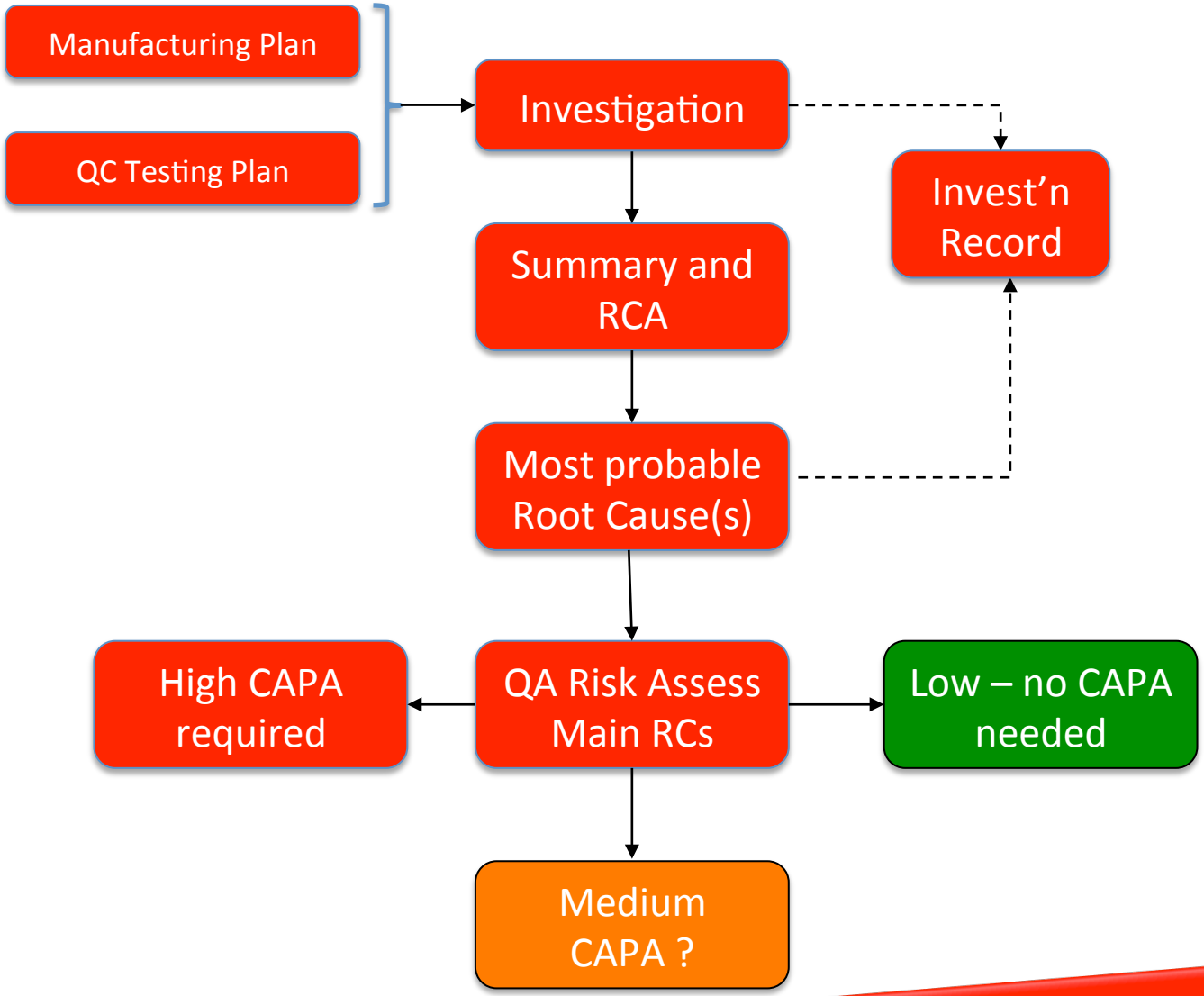
Investigations

- SOP on “Investigations, Root Cause Analysis and CAPA”
- SOP serves all investigations not just Deviations/Events
- Investigation plans should be documented on proformas
  - Manufacturing plan
  - Quality Control / Stability plan
- Plans should examine beyond the immediate event – refer to Event logs and other batches/products
- Assign investigation leads – does not have to be QA

Investigation Tips and Tools

- Not all problems need RCA, or they can be solved simply
- Examine the “scene of the crime”
- Involve an SME
- 7 Management Tools, then 7 Statistical Tools
- Tools should be quickly accessible to users
  - 5 whys / brainstorming
  - Root cause mapping / C&E Diagrams
  - Pareto, Kepner Tregoe, DMAIC
- Last resort – FMEA level approach

Deviation Investigation Flowchart



Investigation Tips

- Do it quickly
- Interview Operators
- Root Cause(s) – silver bullet ?
  - Ineffective training
  - Human Error
  - Re-write the SOP
- Trigger Event (generally obvious)
- Underlying Condition (often obscure)

Root Cause Analysis /Investigations – some tips

- Investigate “in the moment”, not with hindsight.
- Be systematic and objective – don’t focus on silver bullet
- Consider **“Look-back”** and **“Look-forward”**
- “Operator Error - Re-train the operator.”
  - Operator error has at least 7 different causes.
  - In a training system that was possibly flawed, to an SOP that may have generated the error ?

Hard Questions in Investigations

- Natural tendency to limit investigations to the batch in question.
- **No "Look – back" or "Look – forward"**.
  - Look back – previous batches / products affected
  - Look Forward – likely to repeat the problem in the future – what's changed ?
- Regulators rightly expect that these potential consequential issues are assessed and documented.
- Not addressing consequential issues is a surefire way to generate a Warning Letter by FDA and criticism from TGA / PICs Inspectors.

Examples

- 1,500 Litres of Vaccine down the drain
- “This batch has glass in it – it shouldn’t be released”
- OOS low potency for biological – repeat the test
- Blow moulded bottle – base uneven

Deviation Resolution and Release

- **Release:** Deviations should be resolved before release of materials or product.
- Does this also require implementation of CAPA ?
  - Correction – Yes
  - CAPA – if possible but not always feasible
- Two point close out for Deviation / CAPA
    - **Deviation Closed**
    - **CAPA Completed**

Timeframes for Processing Deviations and Investigations

- Deviations reports must be raised within **3 working days** of the event occurring ands submitted to Quality Assurance.
- Batch/ SQuIPP related deviations/incidents must be closed out before any implicated batch is released.
- Close out means that a **batch correction** must be implemented, where warranted.
- All other (non-SquIPP) deviations/incidents should be closed out **within 30 calendar days.**

Assessing Deviation Significance is related to CPPs, CQAs and CSMs

Critical Process Parameter (CPP)

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality

Critical Quality Attribute (CQA)

A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality.

Critical Starting Material (CSM)

Critical Quality Attribute(s) of a Starting Material

Expanded Investigation (Look back and Look forward)

- When investigating a deviations it is not enough to simply review the event is isolation. The investigations should:

- **Look- back** on past batches that may have been compromised by the deviation under review. Examine batch records, test records other deviation records and complaint records. Look back should determine whether any quarantine or hold on related batches should occur or whether batches released to market should be recalled.

- **Look forward** to try and identify whether future batches may be compromised if no CAPA action is taken. This will determine when processing may recommence and what additional controls may be needed.

Outcomes of Deviation Investigations

- **Clear SQuIPP Impact** – a deviation that is likely to have an actual adverse effect on product quality, safety, purity, identity or potency. The deviation is most likely to have an impact on a CPP and/or a CQA.

- **Possible/Probable SQuIPP Impact –** an isolated event or deviation from an approved procedure that may have an unknown effect on a product. The deviations may or may not have an impact on a CPP, but is unlikely to have any impact on a CQA.

- **Clear no SQuIPP Impact** – a deviation that has no actual or a potential adverse effect on product quality, safety or efficacy. The deviation is likely to have no impact on a CPP and/or a CQA.

- **Other** – a deviation from GMP or from a procedure that has very low to no potential impact on product quality or a product CQA / CPP).

Two Things to Keep in Perspective

- The holder of a manufacturing authorisation must manufacture medicinal products so as to ensure that they are fit for their intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy.

- The level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

CAPA and Regulatory Guidance

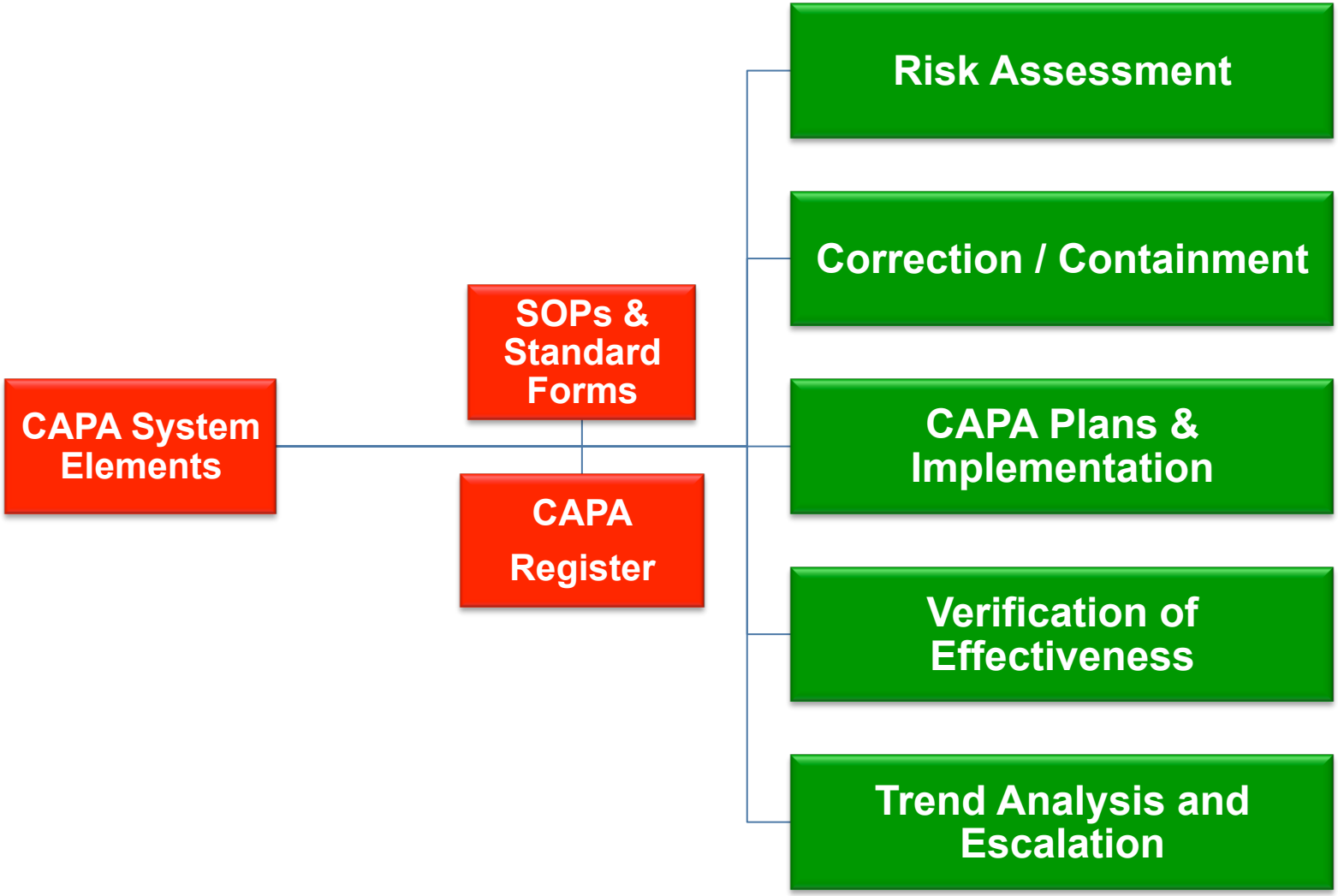
- Drug GMPs have been backward looking. Pharma Industry would do well to study the Medical Device requirements.
- PIC/s cGMPs are pretty light on in terms of CAPA expectations – inspectors are not.
- ICH Q10 provides a significant step up in expectation but not mandated yet.
- FDA regularly reference lack of effective CAPA in warning letters.

ICH Q10 - Corrective and Preventive Action

- Should have a system for implementing CAPAs resulting from investigations of:
  - Complaints and Recalls
  - Product Rejections and Non-conformances
  - Deviations
  - Audits & Regulatory inspection findings
  - Trends from process performance and product quality monitoring

- **"The level of effort and formality of investigation depends on the level of risk"**

Essential Elements of a CAPA system



Important "CAPA" Definitions

Correction: Correction refers to repair, rework or adjustment and relates to the disposition of an existing non-conformity, defect, or other undesirable situation

Corrective Action: Action to eliminate the causes of an existing non-conformity, defect or other undesirable situation in order to prevent recurrence.

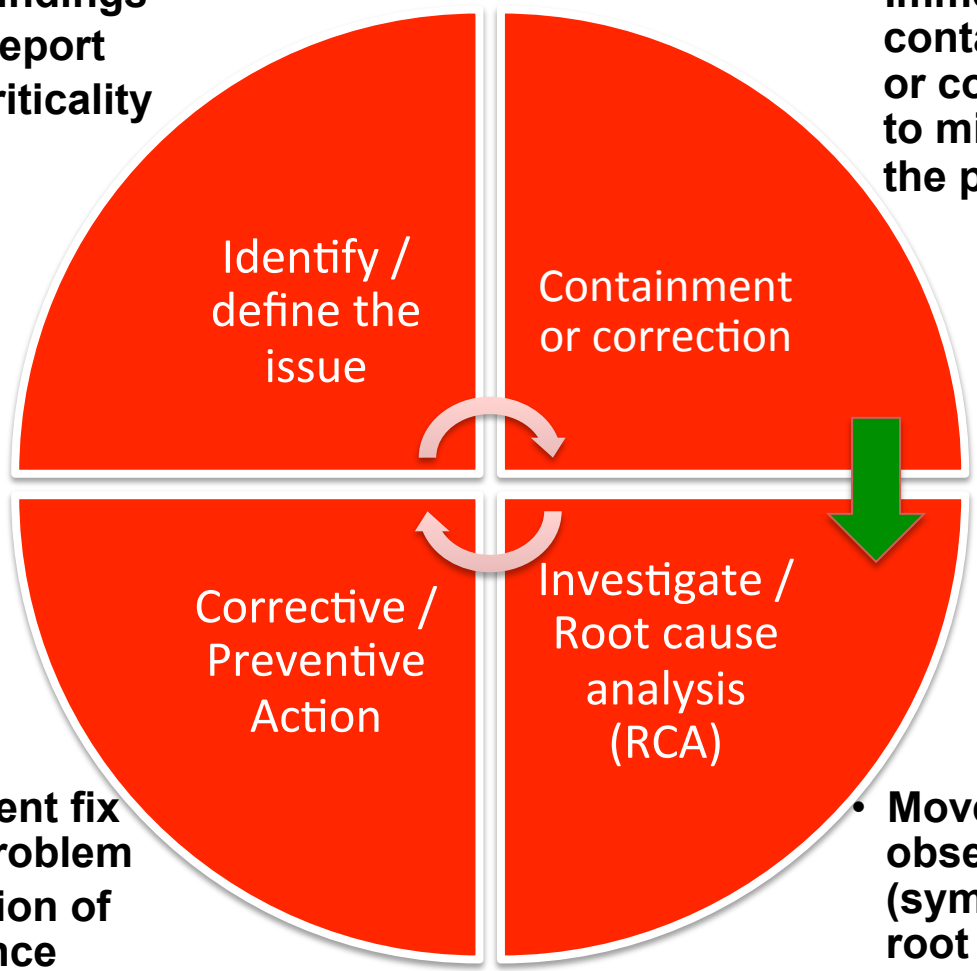
Preventive Action: Action taken to eliminate the cause of a potential non-conformity, defect, or other undesirable situation in order to prevent occurrence

Continuous Improvement: Recurring activity to increase the ability to fulfill requirements.

CAPA Processes

- **Audit findings**
- **Audit report**
- **Rate criticality**

- **Immediate containment or correction to minimise the problem**

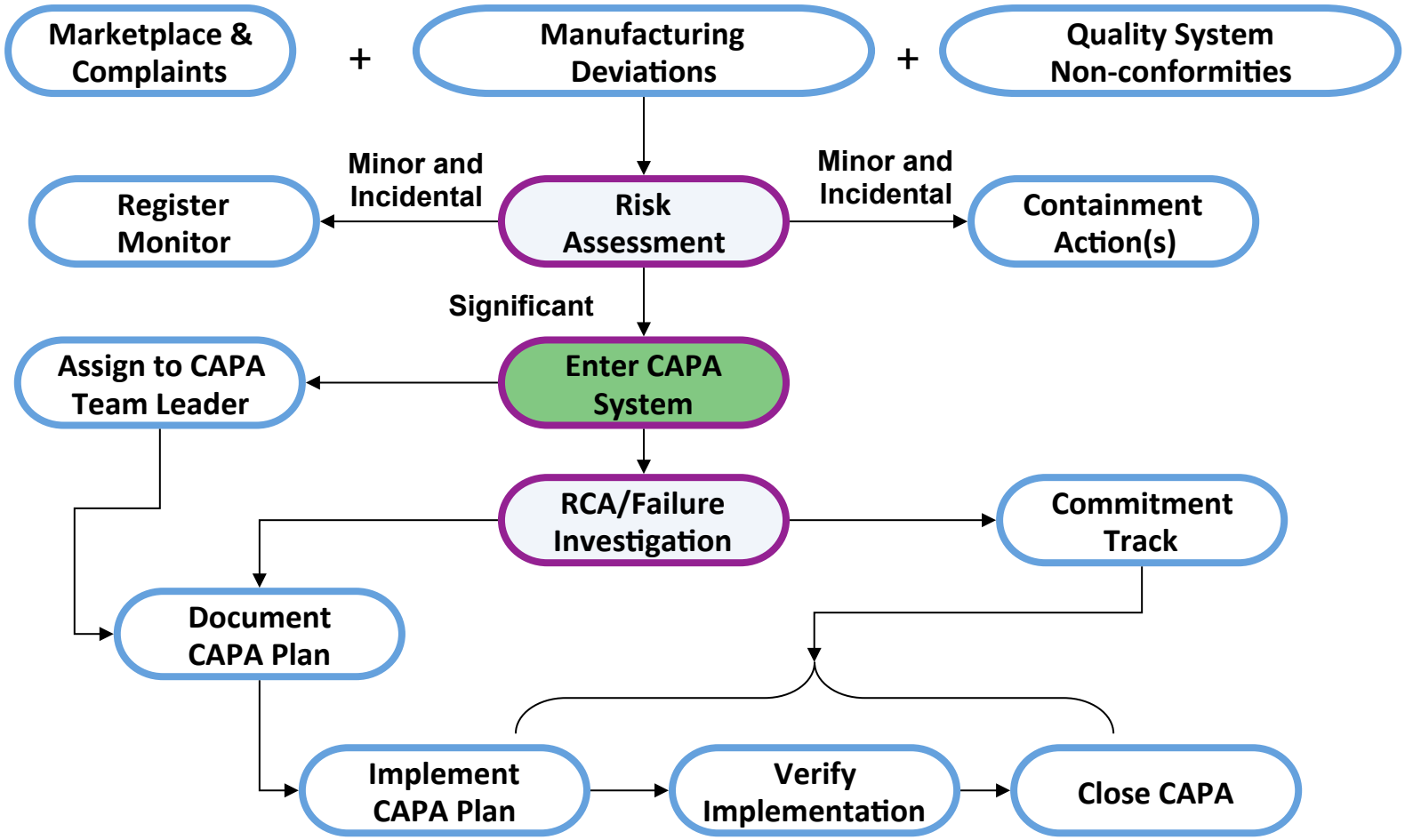


RCA if warranted eg **critical or major deficiency**

- **Permanent fix of the problem**
- **Prevention of recurrence**
- **Verify effective**

- **Move from observation (symptom) to root cause of the problem**

CAPA Management Flowchart



Steve Williams,
Director, CBE Pty Ltd
www.cbe-ap.com.au
☎ +61(0)417116476
✉ steve.williams@cbe-ap.com.au