Centre for Biopharmaceutical Excellence

Managing GMP Deviations Using Quality Risk Management (QRM)

Three Day Program

Monday - Presentations

- Management of Deviations/Investigations and CAPA
- Change Management
- Video and Group Discussion (Trevor)

Tuesday Morning - Presentations

- Sterile Manufacturing GMPs – What Regulators and Inspectors Look For
- Data Integrity

Tuesday Afternoon – Workshops

- Deviations, QRM and CAPA

Thursday – Workshops

- Stream 1 – Change Management and QRM
- Stream 2 - Sterile Manufacturing
- Assessing OOS/OOT for Microbiological Events

Module Topics

- Quality Risk Management
- Deviations and Quality Events
- Investigations
- CAPA and Continuous Improvement

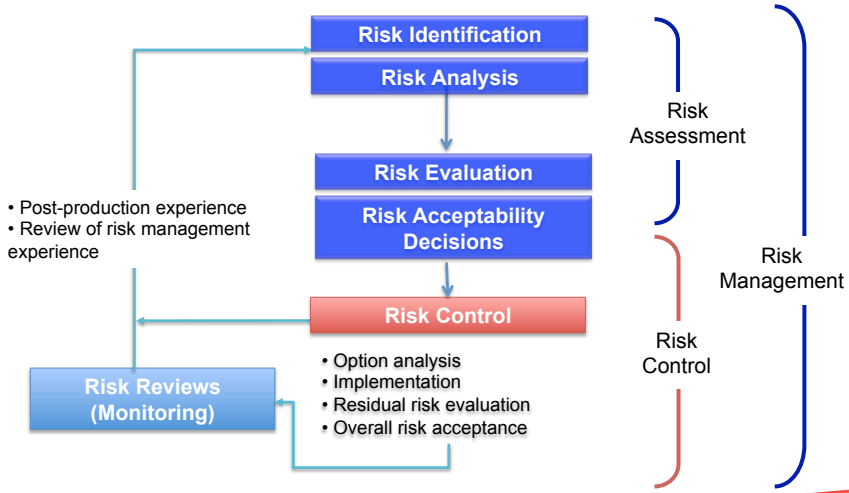
Quality Risk Management Basic Principles Refresher

- QRM is well established in all cGMPs since 2004
- Practiced in most companies, mainly in:
  - Quality Management
  - Qualification and Validation
- ICH Q10 recognises QRM as an enabler or facilitator of good decision making;
- Does not replace Manufacturers GMP obligations;
- ICH Q9/ PICs Annex 20 are standard references;

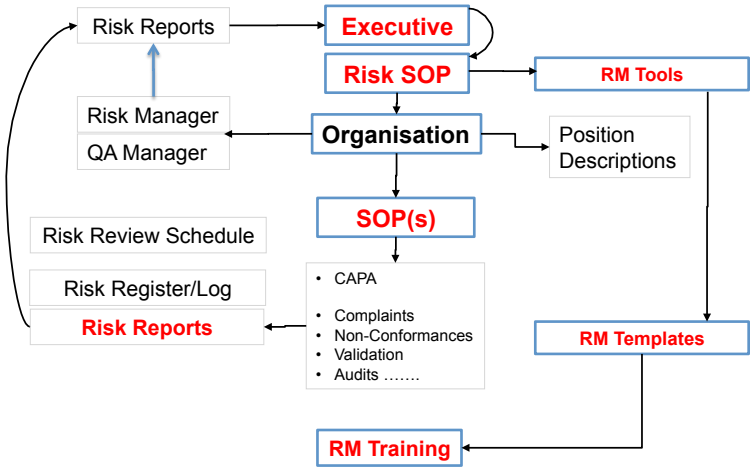
PICs cGMP Annex 20 - Quality Risk Management (QRM)

- "It is commonly understood that *risk* is defined as the combination of the **probability of occurrence** of *harm* and the ***severity*** of that harm."
- It is neither always appropriate nor necessary to use a formal risk management process. Using informal processes is also acceptable.
- QRM does not negate industry's obligation to comply with regulatory requirements

ICH Q9 and ANSI/AAMI/ISO 14971 Risk Model



Risk Management Documentation



QMS Element	Application of QRM - Refer to ICH Q9 / PICs Annex 20	SOP Linkage
1 Audit Programs (Internal and External)	Assign non-conformance criticality ratings based on risk to GMP compliance, or product safety. Evaluate supplier control based on risk	Internal Quality Audits Supplier Assurance Programs
2 Complaints & Recalls	Assign initial risk evaluations to incoming incidents and again after post investigation.	Complaint Management Recall Programs
3 CAPA System	Generally incidents or potential risks are "**qualified"** into the CAPA system.The CAPA systems manages mitigations.	Corrective and Preventive Action (CAPA)
4 Deviations	Initial informal potential risks are assessed. potentially significant risks move to formal deviation assessment.	Deviation Management
5 Quality Defects (Non-conformances)	OOS events are based on risk assessment however the potential for other related Lots to also be defective may be warranted based on a risk assessment.	Out ofecifications (OOS)
6 Computerised Systems	Computerised systems are assessed for risk levels based on GxP criticality and system complexity.	Computerised System Validation Master Plan
7 Validation Programs	The cGMP requires that validation programs be driven by risk assessment (Annex 15 – 1 Principle.)	Qualification Programs Process Validation Revalidation/qualification
8 Change Control	Change control requires an impact assessment based on potential risks to marketing authorisation, compliance, maintenance of the validated state and patient safety.	Change Management
9 Training and Documentation	The depth and extent of training and documentation should be directly related to the criticality of that operation.	GMP Training Programs

ICH Q 9 Risk Assessment

- Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards
- As an aid to clearly defining the risk(s) for risk assessment purposes, three fundamental questions are often helpful:

1. What might go wrong?

2. What are the consequences (severity) if it did go wrong?

3. What is the likelihood (probability) it will go wrong?

Flash Quiz

	Regulatory / GMP Expectation for Risk Management	Your Selection
1	Which of these statements is true (there may be more than one) (a) There is a GMP requirement for a risk SOP but not a Register (b) There is a GMP requirement for a Risk Register but not an SOP (c) Documented risk reports should be reviewed periodically (d) Risk Assessment is more to do with GMP than patient safety	
2	Which of these statements is true (there may be more than one) (a) Applying Risk Management is optional, not mandatory (b) The level of effort should be commensurate with the risk (c) Risk assessments should be documented in some way per GMPs (d) GMPs require us to only conduct reactive risk assessments.	
3	QRM should be applied to deviations and non-conformances only	TRUE/FALSE
4	Risk Management combines Risk Assessment and Risk Control	TRUE/FALSE

Fundamentals of Risk Management

https://www.youtube.com/watch?v=BLAEuVSAIVM

1. What are we trying to achieve ? [Scope and Context]
2. What might affect us ? [Risk Identification]
3. Which risks are the most important ? [Risk Analysis]
4. What should we do about it ? [Risk Control / Mitigation]
5. Did the mitigations work [Mitigation (CAPA) Effectiveness]
6. What changed over time – any new risks ? [Risk Review]

Risk Tools and Techniques

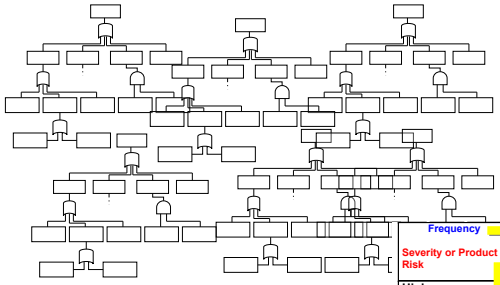
Recognized risk management tools include:

- **Risk ranking and filtering**
- **Basic risk management facilitation methods (flowcharts, check sheets, etc.)**
- **Failure Mode Effects Analysis (FMEA)**
- **Preliminary Hazard Analysis (PHA)**
- Failure Mode, Effects, and Criticality Analysis (FMECA)
- Fault Tree Analysis (FTA)
- Hazard Analysis and Critical Control Points (HACCP)
- Hazard Operability Analysis (HAZOP)
- Supporting statistical tools

The formality of quality risk management should reflect the complexity and/or criticality of the issue to be addressed.

Quantitative and Qualitative Risk Assessment Techniques

Quantitative Approach



A x B x C = a number

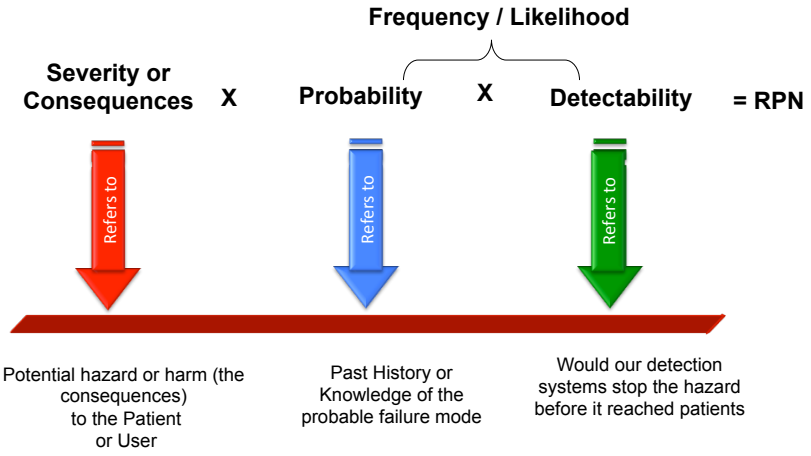
Qualitative Approach

Frequency → / Severity or Product Risk ↓	Rarely (Possible but unlikely to occur)	Occasional	Frequent (Probable – likely to occur)
High likely patient harm /injury or recall of product	Moderate	Major	Critical
Medium Unlikely to cause harm/injury but likely complaints	Minor	Moderate	Major
Low Cosmetic defects only low to very low impact on quality	No Risk	Minor	Moderate

Example Qualitative Risk - Analysis Table

Severity or Product Risk → / Probability ↓	Low Cosmetic defects only low to very low impact on quality	Moderate Unlikely to cause harm/injury but likely complaints	High likely patient harm /injury or recall of product
Frequent (Probable – likely to occur often)	Moderate	Major	Critical
Occasional	Low	Moderate	Major
Rarely (Possible but unlikely to occur)	Negligible Risk	Low	Moderate

Risk Assessment Components - Risk Priority Number (RPN)



Quantitative Risk Tables Example

Ranking	Severity (S)	Probability (P)	Detection (D)
10	Death	More than once a day	Impossible to detect
9	↓	**3 – 4 times a day**	Remote
8	**Permanent injury**	Once a week	**Very slight**
7	↓	Once a month	Slight
6	**Temporary injury**	Once in three month	Low
5	↓	Once in half – one year	Medium
4	Reported/ dissatisfied	Once a year	Moderately high
3	↓	Once in 1 – 3 years	High
2	Notice/ no report	Once in 3 – 5 years	Very High
1	↓	Less than once in 5 years	Virtually certain

Takayoshi Matsumura, Esai Co

Template – Qualitative Risk Assessment

Report #	RAR _ _ - _ _ _ _ _	Report Title:	

Batch #		Product/Process Name		Source Ref #	
Classification/Source	☐ QMS → ☐ Validation ☐ Change ☐ Audit / GMP ☐ Deviation ☐ Non Conformance ☐ Complaint ☐ Supplier Assurance ☐ Product ☐ Materials ☐ Design ☐ Process ☐ Other				
Participants in RA		RA Prepared by:		RA Approved by:	

1 **Statement of the Potential Hazards and Risks** *Provide a brief statement of the potential risk being analysed.* (The background)

2 **Risk Analysis:** *Describe the potential consequences (patient harms), the likelihood the hazard / failure mode would occur and whether it would be detected*

Risk #	State Potential Hazard(s) Description /Failure Mode	Patient / GMP Consequences Rating	Likelihood and Detectability Assessment	Likelihood & Detectability Rating	Final Potential Risk Rating**
#1			**Likelihood:**		
			Detectability: *(if relevant)*		
#2			**Likelihood:**		
			Detectability: *(if relevant)*		
#3			**Likelihood:**		
			Detectability: *(if relevant)*		

** *Assess the potential risk prior to any mitigation action.*

EXAMPLE ONLY

Qualitative RA Example

Report #	RAR 16 - 008	Report Title:	Customer Complaint Leaking Bottle of Cough Syrup (Multidose cvontainer)

Batch #	123	Product/Process Name	Brilliant Cough Syrup (250mL) Code XYZ	Source Ref #	CC - # 012
Classification/Source	☐ QMS → ☐ Validation ☐ Change ☐ Audit / GMP ☐ Deviation ☐ Non Conformance X Complaint ☐ Supplier Assurance ☐ Product ☐ Materials ☐ Design ☐ Process ☐ Other				
Participants in RA	SW, EL, RK, TT	RA Prepared by:	QC Manager	RA Approved by:	QA Manager

Statement of the Potential Hazards and Risks

A customer complained of a leaking vial from Vaccine Batch XYZ -123 received on 29 Feb 16. The container was returned and the leak verified. The customer was not injured. There may be other containers in the market with similar problems and any defective unit may be contaminated or lose potency.

Risk #	State Potential Hazard(s) Description /Failure Mode	Patient / GMP Consequences Rating	Likelihood and Detectability Assessment	Likelihood & Detectability Rating	Final Potential Risk Rating**
#1	**Hazard:** Potential loss of sterility or particle contamination **Harm:** Patient could be injected with non-sterile vaccine – sepsis	4 Potential acute infection and likely will refer to Doctor	**Likelihood:** No related complaints and batch near shelf-life. Passed. **Detectability:** retention samples checked - OK.	2	8 **(Medium Risk)** **Action Optional**
#2	**Hazard:** Potential loss of efficacy/ stability of the vial **Harm:** Patient may not receive correct dosage – ineffective vaccine.	3 In-effective treatment	**Likelihood:** No related complaints and batch near shelf-life. Passed. **Detectability:** retention samples checked – OK.	2	6 **(Low Risk)** **Action Not needed**

Preliminary Hazard Analysis (PHA)

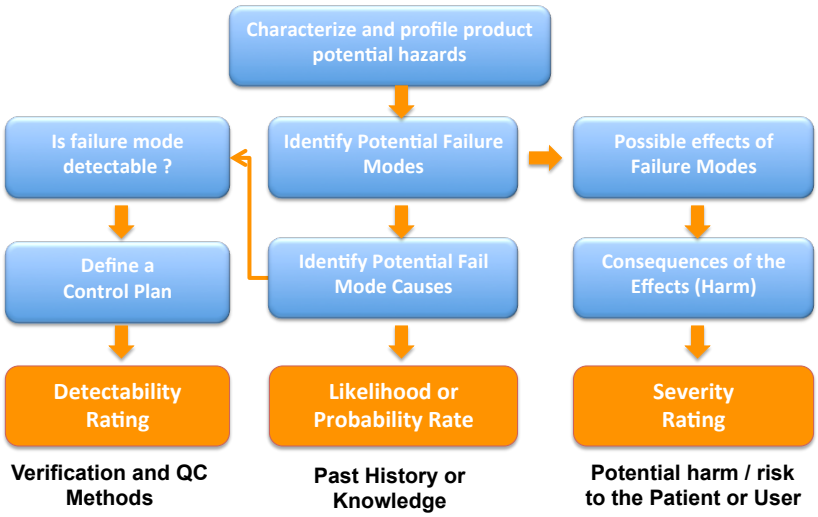
PHA is a tool of analysis based on applying prior experience or knowledge of a hazard or failure to identify future hazards, hazardous situations and events that might cause harm, as well as to estimate their probability of occurrence for a given activity, facility, product or system.

	Potential Risks for Current Situation							Mitigations / Controls		Revised Post Mitigation			
Process Step	Potential Risk	Consequences	Potential Causes (Likelihood of Occurrence)	Likelihood	Current Controls and/ or Detectability	Current Control	RPN	Recommended Mitigation Actions (Proposed Controls)	Responsible for Actions)	Consequences	Likelihood	Lack of Detect	Revised RPN**
A1													
A2													
Etc.													

FMEA – Process Steps

1. Assemble the team - Key stakeholders and players
2. Gather background data
   - **Flowchart the process**
   - Obtain known facts and data
3. Team brainstorm - Potential failure modes – where, when, circumstances
4. Identify failure effects - extent, frequency, severity, ease of detection
5. Identify root cause of failure
6. Determine current controls
7. Identify corrective actions

How is an "FMEA Risk Analysis" done ?



Risk Acceptance Criteria (based on analysis)

Risk Classification	Risk Acceptance Criteria
UNACCEPTABLE	Risk is UNACCEPTABLE – action must be taken to mitigate the concern AS SOON AS POSSIBLE. Note when a health hazard (Consequences) of 5 is determined, action is expected independent of the likelihood of occurrence.
HIGH	Risk is HIGH – action should be taken to mitigate the concern. Any decision to not take actions must be documented and fully justified.
MEDIUM	Risk is MEDIUM – action is optional and considered with respect to the overall benefit. The decision to not take action should be documented if classified as MEDIUM
LOW or NEGLIGIBLE	Risk is LOW or NEGLIGIBLE – action is likely not warranted.

Quality Risk Management (QRM)

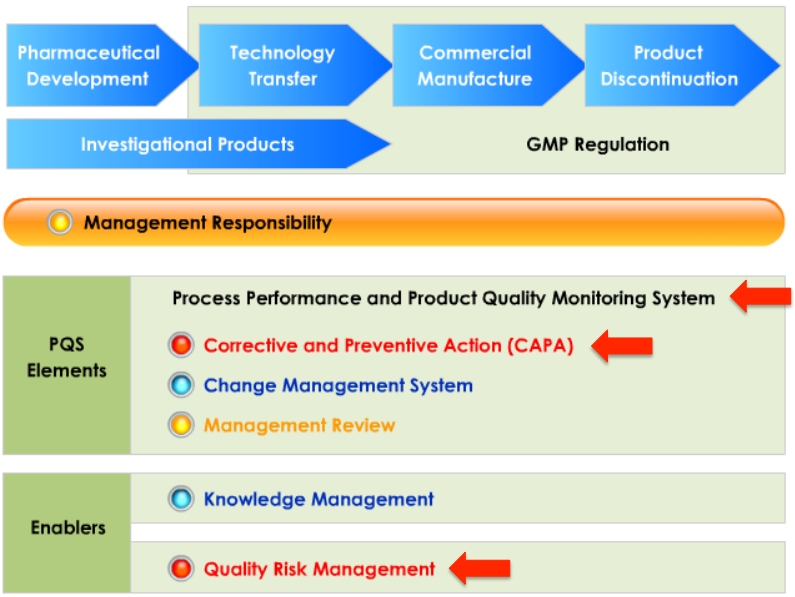
- Applying QRM enables better understanding of the dimensions of a problem
- Provides a systematic approach to escalating and prioritising significant events

Flash Quiz

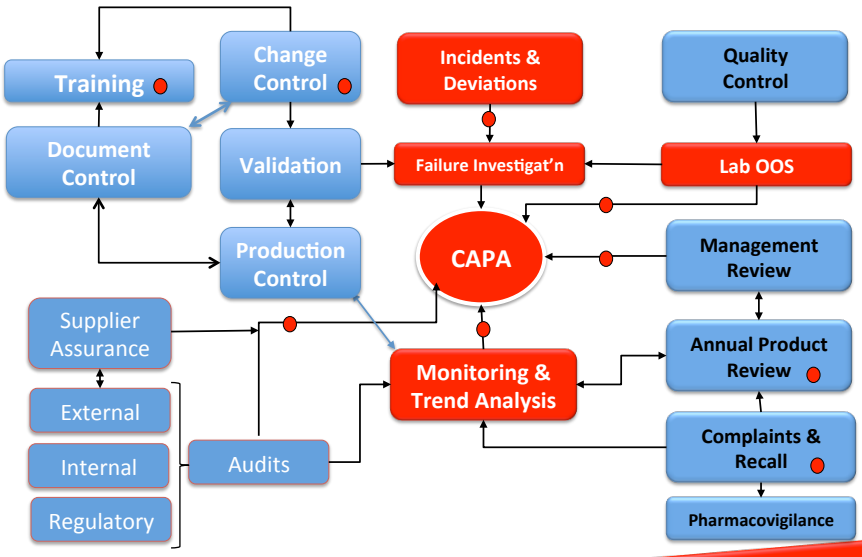
	What do Regulatory Inspectors Look For when assessing QRM ?	Your Selection
1	Which of these statements is true (there may be more than one) (a) The company must have an independent risk advisor who conducts all risk assessments (b) PICs look to see where RA justifies failure to meet GMP requirements or product specifications (c) PICs will not review the companies template structure	
2	Which of these statements is true (there may be more than one) (a) Regulators expect that the QRM system is reviewed for effectiveness (b) Risk Assessments are supported by objective evidence (c) Risk assessments are supported by the QA Manager/AP opinion (d) Justifications for conclusions are expected in risk assessments	
3	Quantitative RAs are preferred over Qualitative by Inspectors	TRUE/FALSE
4	PICs Annex 20/ICH Q9 recommends flowcharts, decision trees and check-sheets be used as assessment tools	TRUE/FALSE

Deviations, Investigations and CAPA

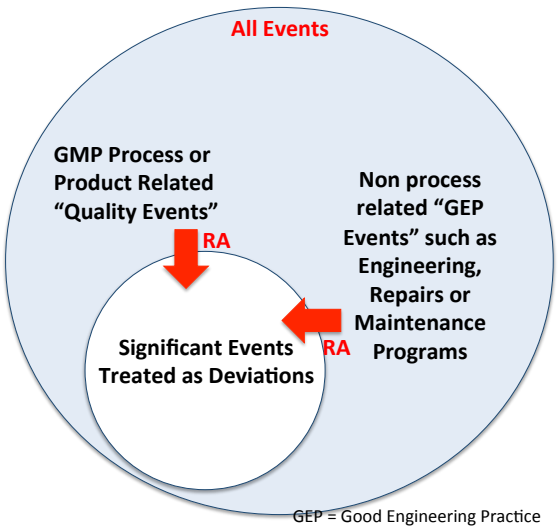
ICH Q10 - Pharmaceutical Quality System



How does a Quality System Fit Together ?



Assessing Quality Events and Deviations



GEP = Good Engineering Practice

PICs Expectation

- All events are recorded
  - GMP events on a register or log
  - GEP events in engineering records
- Expect review of GEP records to make sure they are not missed;
- **Significant** events are investigated as deviations

WHO TRS986 Annex 2 Principles 1.5 (s)

Requirements are equivalent to PICs

FDA View on Quality Metrics

Indicator	Metric
Lot Acceptance Rate	Number of lots rejected in a year / number of lots produced
Right First Time Rate	**Number of deviations / lot**
Complaint Rate	Number valid complaints/number of lots released per year
Invalidated (OOS) Rate	Number of OOS test results invalidated /tests performed
Annual Product Review (APR) on Time Rate	Number of APRs generated within 30 days of annual due date
Management Engagement	Most senior manager that signed each annual product review
Process capability or performance index	Whether performed for each critical quality attribute as part of that product's APR.
Corrective and Preventative Action (CAPA) Rate	Number of CAPAs that were initiated due to an APR, divided by the total number of APRs generated.

Top Critical/Major Defect Areas

MHRA

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.

GMP Deviation Requirements

- **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 of products;
- **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.

WHO Guidance Deviation Handling and Risk Assessment (2013)

An efficient deviation handling system, should implement a mechanism to discriminate events based on their relevance and to objectively categorize them, concentrating resources and efforts in good quality investigations of the root causes of relevant deviations.

A sequence of steps may be identified when handling events and possible deviations:

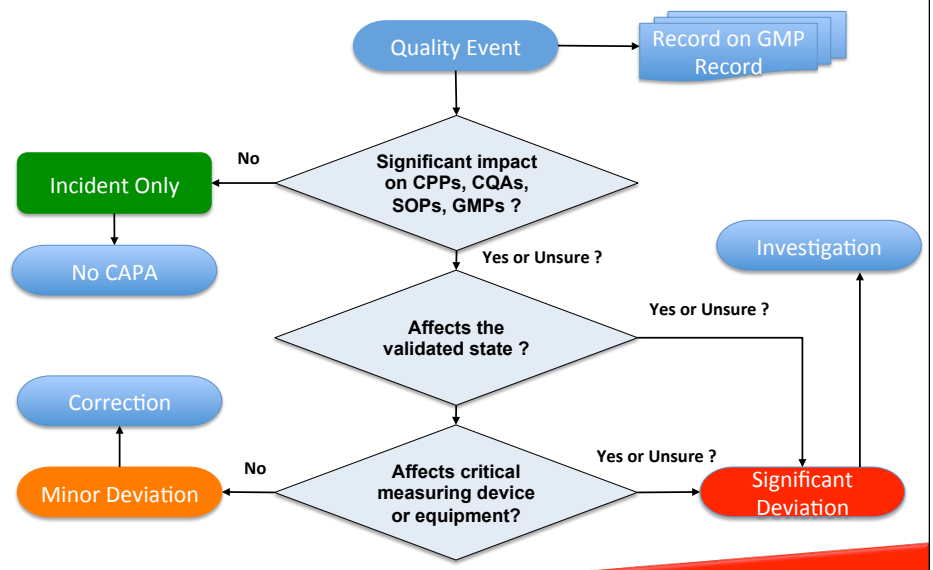
- Event Detection
- Decision Making Process / Deviation Categorization
- Deviation Treatment
- Root cause investigation
- CAPA

WHO Guidance Deviation Handling and Risk Assessment (2013)

- The decision tree described in **Diagram 1** is a simplified risk assessment that answers the following questions when an event is encountered:
- a. Can the event affect a product attribute, manufacturing operational parameter or the product's quality?
- b. Does the event contradict or omit a requirement or instruction contemplated in any kind of approved written procedure or specification?

WHO Guidance Deviation Handling and Risk Assessment (2013)

Using a Decision Tree To Risk Assess Events and Deviations



WHO Guidance Deviation Handling and Risk Assessment (2013)

- **Incidents** (Quality Events) are documented and filed. No action is required.
- **Minor deviations** are normally addressed by corrections. Investigations are not required.
- **Major or critical deviations (Significant)** usually require an enhanced, thorough and objective description which needs to be documented. An adequate description associated to the deviation is essential in order to perform a meaningful investigation. CAPA is required

WHO Guidance Deviation Handling and Risk Assessment (2013)

- The term “planned deviation” is frequently used to describe a decision to carry out a process in a different way from which it is established in a SOP, Method or Manufacturing Batch Record (e.g., a reprocess) due to an unforeseen event.
- Planned deviations need to be fully documented and justified. Usually, planned deviations is associated to onetime events, and change control to permanent changes.

PICs cGMP Expectations for Deviations

- 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 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

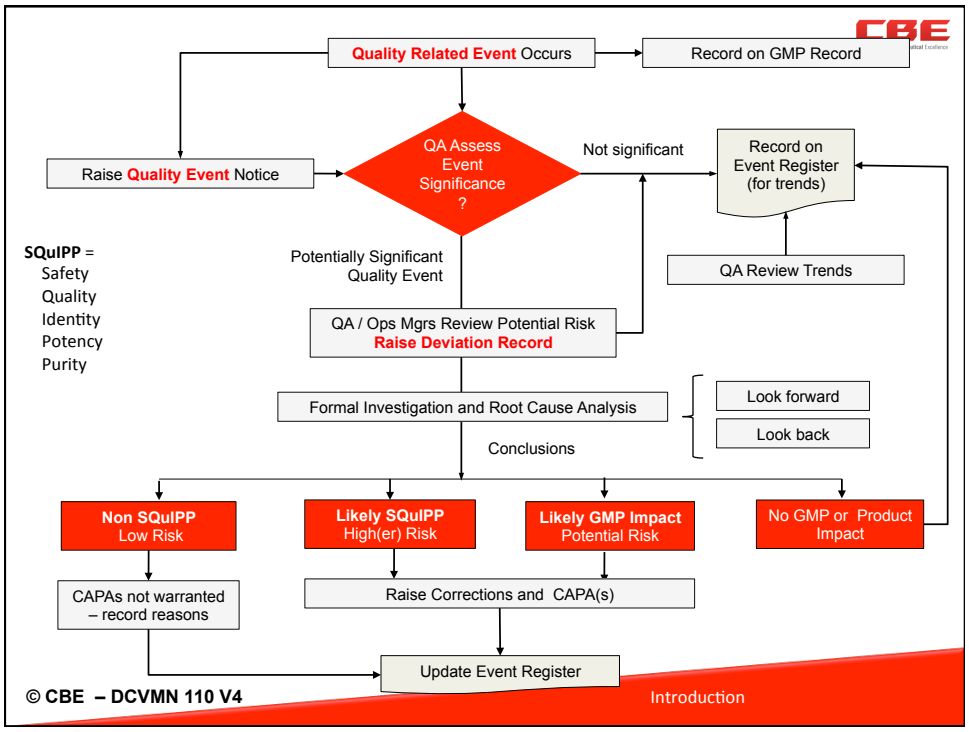
Alert and Responsive to Events

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



Categorise Event Categories for Deviation Trending

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

Example Only

Preliminary Risk Assessment

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 ?

Example Only

Example of Checksheet for Preliminary RA

HEPA Filter Failure in Grade B Cleanroom – approx. 10% of filters fail when tested.

1	Likely the event could impact Sterility Assurance, bioburden or endotoxin **?**	**Yes**
2	Does the event result in an excursion from registered details for this product ?	No
3	Likely the event could cause physical contamination or cross contamination ?	No
4	Likely the event could cause loss of identity or traceability ?	No
5	Likely the event could result in an out of specification result, if tested ?	No
6	Likely the event could cause defects in container closure integrity ?	No
7	Likely the event could affect product quality or stability in the marketplace ?	No
8	Is the event related to a GMP non-conformance or outside the "validated state" ?	**Yes**
9	Could this event impact batches already released to the marketplace ?	No
10	Could this event impact SQuIPP for future batches, if not corrected ?	**Yes**
11	Is this event part of a trend ? (Review the Deviation / Quality Event Trend register)	**Yes**
12	Does this event impact a CPP or a CQA ?	No

Examples - Risk Assessment for Events

(Use the checksheet to decide if a Deviation/ investigation is needed)

Event	Conclusion
Circular Temperature chart recorder did not record – operator did not press pen down sufficiently. Temperature of processing missing at start of the bulk mixing step.	CPP impacted but is a WPP and step has been validated Dev (Yes) Invest. (No)
API ingredients were added out of order to the bulk mix. The order of addition is part of the process validation. The batch passed all testing.	Validated state is impacted Dev (Yes) Invest. (Yes)
Calculated yield below limits (was 90% and limit was > 95%) Cause was a spillage of one drying tray.	SQuIPP is not impacted Dev (No) Invest. (No)
Outer carton – some expiry dates were not printed on the carton. The batch was 100% sorted and overprinted defects.	SQuIPP maybe impacted (identity) Dev (Yes) Invest. (Yes)
2 - 8oC cold storage temperature above limit for 48 hours - Alarm did not activate.	SQuIPP maybe impacted (Potency) Dev (Yes) Invest. (Yes)

Recording and Evaluating Deviations

Most important to record the deviation quickly (<2 days) 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.

Flash Quiz

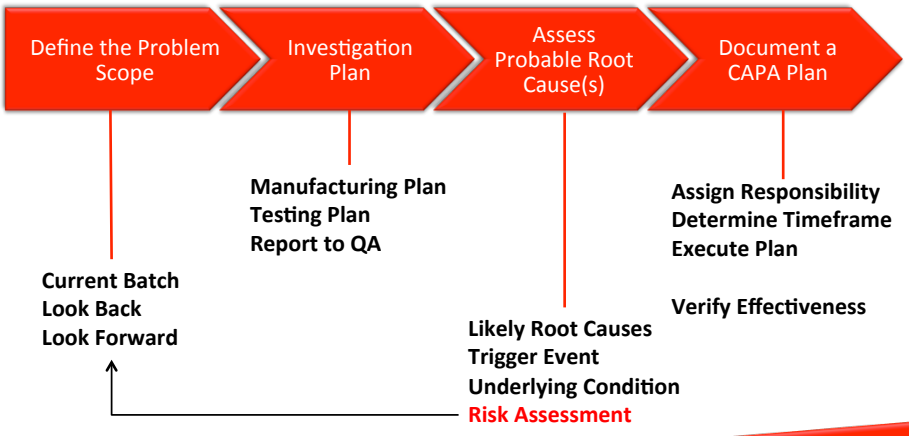
	Deviation Management	Your Selection
1	(a) GMPs require that each deviation or event is recorded (b) Quality events can be risk assessed before escalating to a deviation (c) Once a Root Cause Analysis done the extent of the risk can be better understood	
2	Deviations should be reviewed by: (a) Finance (b) IT Manager (c) AP or member of QA team (d) User Department Manager	
3	Not all quality events result in a deviation but almost all deviations originate fro ma quality event	TRUE/FALSE
4	Risk assessment is not needed for deviations as as they are a GMP non-conformance and action must be taken.	TRUE/FALSE

Investigations and Root Cause Analysis

https://www.youtube.com/watch?v=w3TqOp9-0L8

Investigations

- SOP on "Investigations, Root Cause Analysis and CAPA



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

5 Why Exercise

https://www.youtube.com/watch?v=1f1_kXDXoAQ

- Lets try and get the root cause of something simple:

“Why are you attending training this week”

1. Ask why did this happen ? …….. Get an answer
2. Ask why again to the answer …… Get an answer
3. Repeat 3 more times if needed

Does this final answer look like a reasonable root cause ?

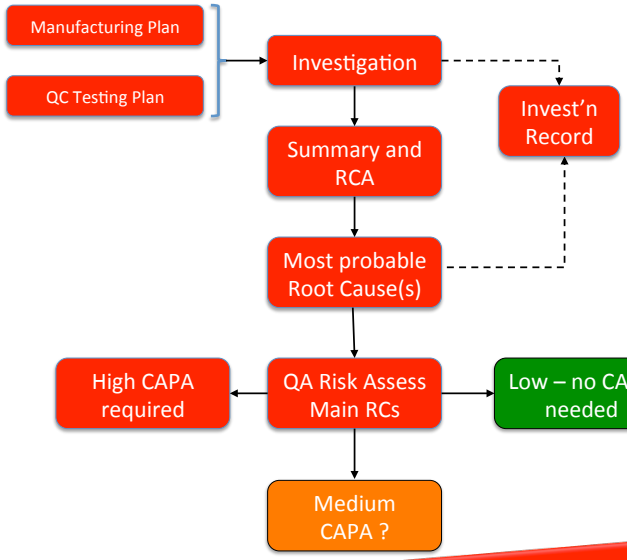
Root Cause Analysis /Investigations – some tips

- 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 ?

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)

Investigation Flowchart



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 WHO/ PICs Inspectors.

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, hold or recall on related batches is needed.

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.

Does the deviation impact these ?

- **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. (ICH Q8)
- **CQA:** A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality. (ICH Q8)
- **CSM:** Critical Starting Material – A starting material that influences a CQA
- **WPP:** A critical process parameter that is robust to operating changes. Would a reasonable excursion (e.g double the operating range) likely impact a CQA ?

Flash Quiz

	Deviation Investigations	Your Selection
1	(a) The decision to investigate an event is driven by risk assessment (b) Investigations can be informal i.e not documented (c) Once a Root Cause Analysis done the extent of the risk can be better understood	
2	Investigation reports should be reviewed by: (a) Finance (b) IT Manager (c) AP or member of QA team (d) User Department Manager	
3	"Look back" and "Look forward" is only required when the deviations is classified as Minor	TRUE/FALSE
4	A Manufacturing and Testing Investigation Plan should be documented	TRUE/FALSE

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

Deviation Resolution and Release

- **Release:** Deviations should be resolved before release of materials or product.
- Does this also require implementation of CAPA ?
  - Correction is required before release under GMPs
  - CAPA – Depends on the risk – a corrective action may last months.
- Two point close out for Deviation / CAPA
  - **Deviation Closed**
  - **CAPA Completed**

Timeframes for Processing Deviations and Investigations

- Deviations reports should be raised within **2 working days** of the event occurring and 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.**

Outcomes of Deviation Investigations

- **Clear SQuIPP Impact (High Risk)**

  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/Potential SQuIPP Impact (Moderate Risk)**

  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.

- **No SQuIPP Impact (Moderate / Low Risk)**

  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 – (Negligible Risk)**

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

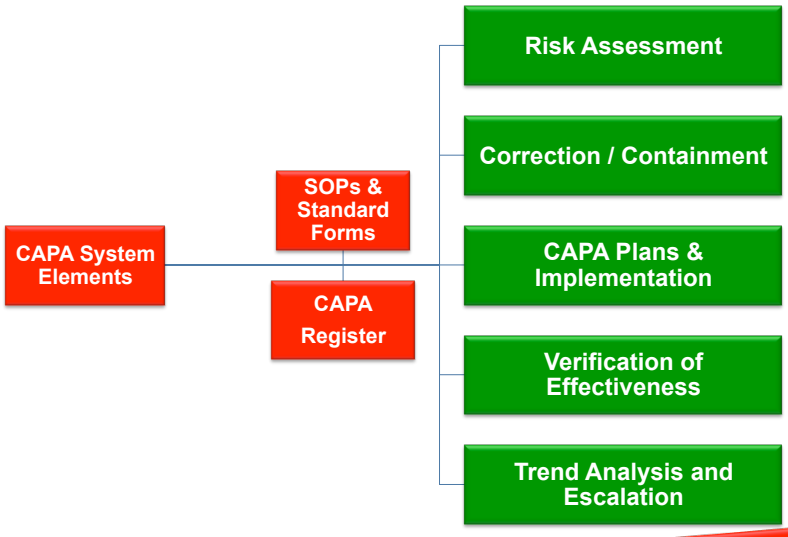
CAPA and Regulatory Guidance

- 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

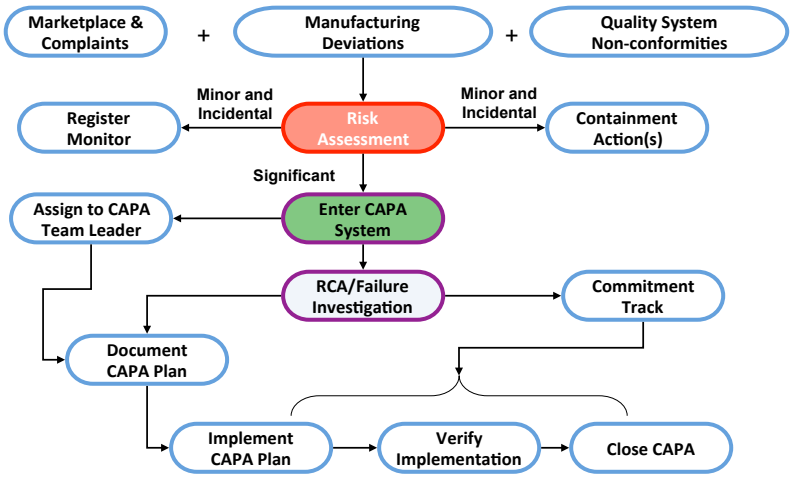
Correction: Correction refers to repair, rework or adjustment and relates to the disposition of an existing non-conformity, defect, or other undesirable situation

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

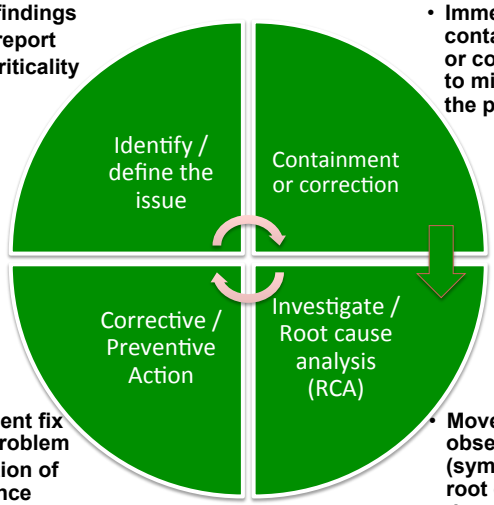
Continuous Improvement: Recurring activity to increase the ability to fulfill requirements.

CAPA Management Flowchart



CAPA Processes

- Audit findings
- Audit report
- Rate criticality



- Immediate containment or correction to minimise the problem

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

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

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

GMP Expectations around CAPAs

- Regulators look to see if CAPA close out is effective and timely;
- CAPA Plans must be documented with assigned responsibility
- CAPAs should have a nominated target date e.g within 30 days;
- CAPA progress should be tracked in Quality Metrics e.g. 90% of CAPAs closed out on time;

Corrective And Preventative Action Record

CAPA #		CAPA Title	

Refer to SOP xxxx for instructions about how to complete this form.

Section 1 – CAPA Source

This record summarises the agreed action as a result of a significant Quality Event (QE), Deviation (DR, Investigation (INV) or risk assessment. It may be used stand alone or as a result of an assessment of deviations, audits, complaints, vendor assessments or laboratory OOS.

CAPA Source	**INV #**	**CAPA Dept Responsibility**	
	Other:	**Target Completion Date**	
Origin Date		**Actual Completion Date**	
Problem Statement			

Section 2 – CAPA Actions

Correction for Current Event or Incident (Describe action taken to correct what happened)			
Correction Completed By		**Date:**	

Is a system based Corrective Action required?	Yes/ /No
Is Preventative action required?	Yes/ /No

If above two questions are answered "No", this report may be closed.

Closed by QA	**Name**	**Signature**	**Date**

Proposed Corrective Actions (Tasks)		By:	**Target Date**
1			
Corrective Action Plan Approved (QA sign)		**Date**	
Corrective Action Completed By		**Date:**	

Corrective And Preventative Action Record

CAPA #		CAPA Title	

Preventative Actions

Proposed Preventative Actions (Tasks)		By:	**Target Date**
1			
2			
3			
Preventative Action Plan Approved (QA sign)		**Date**	
Preventative Action Completed By		**Date:**	

Section 3 – Close Out (Effectiveness) Check

Evidence of Satisfactory Implementation of Corrective or Preventative Action/Close Out
Have the identified risks been mitigated to an acceptable level?

Evidence Reviewed & Approved by QA	**Name**	**Signature**	**Date** *(Copy date to front page)*

Flash Quiz

	Corrective and Preventive Action (CAPA)	Your Selection
1	(a) Verifying CAPA effectiveness is expected for major deviations (b) QA should implement all CAPAs (c) QA should oversee the implementation of CAPAs (d) CAPAs should have a target close out date	
2	CAPA Plans should be reviewed by: (a) Finance (b) IT Manager (c) AP or member of QA team (d) User Department Manager	
3	CAPA close out time is an important Quality Metric	TRUE/FALSE
4	CAPAs should all be closed out within 20 days	TRUE/FALSE

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