Pharmaceutical Quality Risk Management

What will be covered

- ICH-Q9 and WHO-TRS 981
- QRM and Quality System
- Applying QRM to Devaitions, CAPA, and CSV
- Application of QRM to Bulk Antigen PV

Some Useful Reference Documents

- ICH Q10 - Pharmaceutical Quality System
- ICH Q8 – Pharmaceutical Product Development
- ICH Q9 - Risk Management in Pharmaceuticals
- PIC/S cGMP Chapter 1 – Clause 1.5 and 1.6
- PICs Annex 20 - Quality Risk Management
- ISO/IEC Guide 73:2002 - Risk management - Vocabulary - Guidelines for use in standards.
- ISO31000 - Risk management — Principles and guidelines
- ISO31010 - Risk management – Risk assessment techniques

Some Key Definitions

Risk Combination of the **probability of occurrence** of harm and the **severity** of that harm (ISO/IEC Guide 51:1999, definition 3.2)

Hazard Potential source of HARM (ISO/IEC Guide 51:1999, definition 3.5)

Hazardous situation Circumstance in which people, property, or the environment are exposed to one or more hazard(s)

Harm Physical injury or damage to health of people, or damage to property or the environment (ISO/IEC Guide 51:1999, definition 3.1)

Severity Measure of the possible consequences of a hazard

Risk Management File The set of records and other documents, not necessarily contiguous, that are produced by a risk management process (ANSI/AAMI/ISO 14971: definition 2.19)

Some Key Definitions

Risk analysis

- systematic use of available information to identify hazards and to estimate the risk. Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.

Risk evaluation

- process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk

Risk criteria

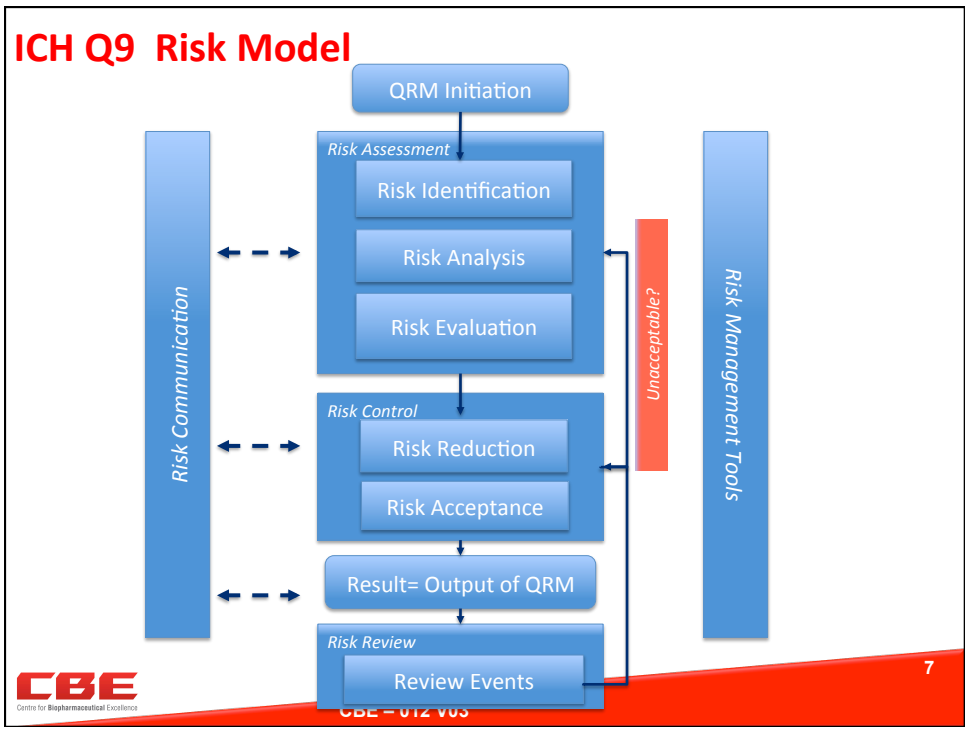
- terms of reference by which the significance of risk is assessed

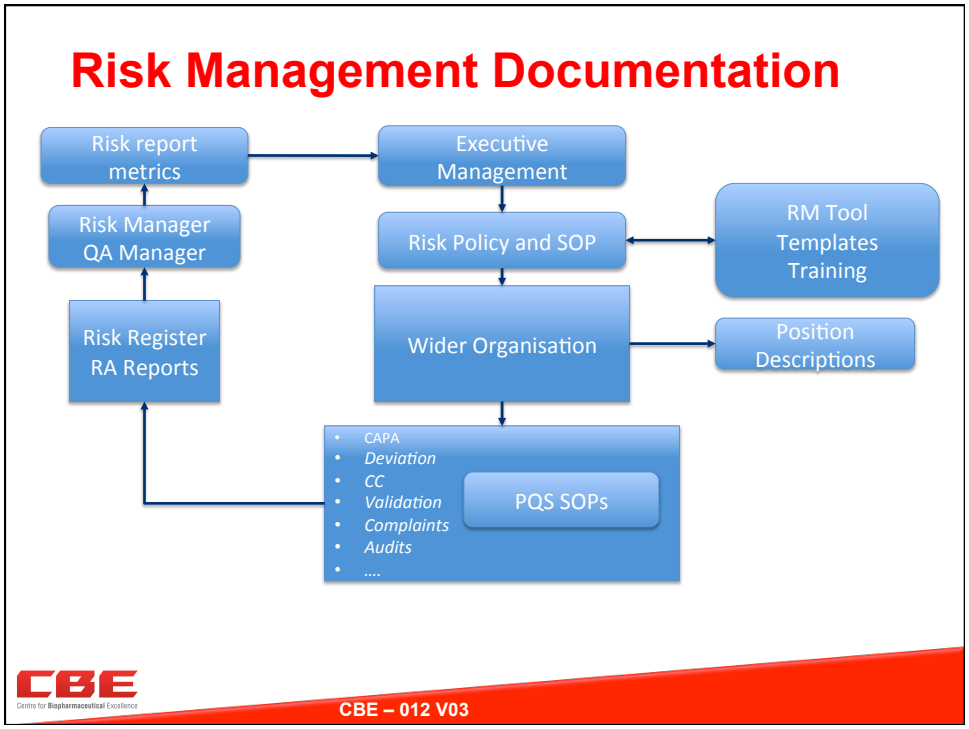
Risk reduction

- actions taken to lessen the **likelihood**, negate **consequences**, or both, associated with a **risk.**

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 Risk Model
QRM Initiation
Risk Assessment
Risk Identification
Risk Analysis
Risk Evaluation
Risk Control
Risk Reduction
Risk Acceptance
Result= Output of QRM
Risk Review
Review Events
Unacceptable?
Risk Communication
Risk Management Tools
7
CBE – 012 V03


Risk Management Documentation
Risk report metrics
Executive Management
Risk Manager QA Manager
Risk Policy and SOP
RM Tool Templates Training
Risk Register RA Reports
Wider Organisation
Position Descriptions
CAPA
Deviation
CC
Validation
Complaints
Audits
....
PQS SOPs
CBE – 012 V03

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 of Specifications (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

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PICS cGMPs – Basics

As Annex 20 represents a voluntary standard, PICs relies mainly on the corresponding mandatory articles of Chapter 1 and Annex 15 of the PIC/S GMP Guide.

1.5 Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the medicinal product. It can be applied both proactively and retrospectively.

1.6 The quality risk management system should ensure that:

- the evaluation of the risk to quality is based on scientific knowledge, experience with the process and ultimately links to the protection of the patient;
- the level of effort, formality and documentation of the quality risk management process is commensurate with the level of risk.

PICs/EU Expectations

Should a company have a procedure to describe how it approaches QRM related to manufacture and GMP?

Yes, the procedure should be integrated with the quality system and apply **to planned** and **unplanned** risk assessments. It is an expectation of Chapter 1 that companies embody quality risk management.

Should sites have a formal risk register and management process?

Recommendation that a risk register is established which should list all key risks identified

- summarize how these have been mitigated and record the current risk level.
- Same approach as index/lists of complaints received or deviations recorded
- Identify if the risk is considered finite (one off) or dynamic (ongoing risk) and thus what ongoing review is required.

A formal review process is expected for QRM and the findings and status from risk assessments – this may be incorporated into the quality management review process.

Regulator View: key attributes of a good risk assessment?

- Ultimately be linked to the protection of the patient;
- Clearly identify the process being assessed i.e what the harm/ risk is and what the impact could be on the patient;
- Take full account of current scientific knowledge;
- Be facilitated by people with experience in the risk assessment process and knowledge of the process/product/ issue;
- Does not include any unjustified assumptions;
- Identify all reasonably expected risks and their mitigations;
- Be documented to an appropriate level.

Difference between a Planned (Proactive) and Unplanned (Reactive) risk assessment?

- A **planned or proactive** risk assessment is one that is conducted in advance of conducting an activity. Proactive RAs allow for opportunity to design risks out of a product or process, or build mitigations in. Can also be used in change management, validation etc.
- An **unplanned or reactive** risk assessment is one that is conducted to assess the potential impact of a situation that has already occurred, eg impact of a deviation or complaint.

Sources of Potential Risk

Reactive sources of risk	Proactive sources of risk
• QMS metrics • Complaints & ADEs • Deviations & Incidents • Failure investigations • Internal / External Audits	• QMS trend analysis • Annual Product Reviews • Management /Quality Reviews • Change Controls • Internal / External Audits • Validation Projects • Revised Process Design

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?

PICS pi-031 (2012) – Aide Memoire Implementation Expectations

The basis of any valuable risk assessment is **scientific knowledge and experience** with the process being assessed. The basis for the evaluation of the identified and analysed risks is defined by the risk to the patient:

- Evidence for effectiveness of risk mitigation should be available;
- Where specific risk elements are discounted this should be supported by appropriate rationale;
- Evidence supports the decisions made.

Unjustified assumptions, incomplete risk identification and lack of experience lead to **inappropriate conclusions.**

PICS pi-031 (2012) – Aide Memoire
(What GMP Inspectors Look For!)

- Inclusion of unjustified assumptions;
- Ultimately linked to the patient;
- RAs are performed by experienced staff;
- Conducted in a systematic manner and supported by appropriate evidence for risk mitigation;
- Ensures that key steps and decisions are documented with a formality that is commensurate with the level of risk;
- Are periodically reviewed for currency and effectiveness;
- Do the conclusions reflect the level of risk to the patient?

PICS pi-031 (2012) – Aide Memoire
(What GMP Inspectors Look For!)

Is there any evidence of QRM being used inappropriately such as:

- To justify failure to meet regulatory requirements and commitments.
- To release batches to market that fall into the category above or to justify increased risk to patient safety from batch deviations.

- Is there a robust system to ensure that all the risk reduction measures (by mitigation or avoidance) have really been implemented in the manner they appear in the risk assessment?

- Are RA reports periodically reviewed for currency ?

PICS pi-031 (2012) – Aide Memoire
(Pharmaceutical Quality System Integration)

- Is there a high level controlled document describing the company's policies and approach to QRM?

- Key attributes of the high level SOP:
  - Evidence of senior management commitment to QRM
  - QRM activities are monitored/reviewed for effectiveness
  - QRM principles are incorporated into GMP training
  - QRM in integrated into the QS, including in the change system.

Flash Quiz

	What do PICs Inspectors Look For ?	Your Selection
1	Which one of these statements is true. (a) Risk management is practiced by the QA team. It's not the role of production. (b) ICHQ9 and PICs Annex 20 are specific requirements for risk assessment (c) Risk management is a new requirement- its been required only last two years. (d) Risk management is not applicable to processes- they are managed by validation	
2	Which of these statements is true (there may be more than one) (a) PICs 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 (d) Justifications for conclusions are expected in risk assessments	
3	Quantitative RAs are preferred over Qualitative by PICs Inspectors	TRUE/FALSE

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

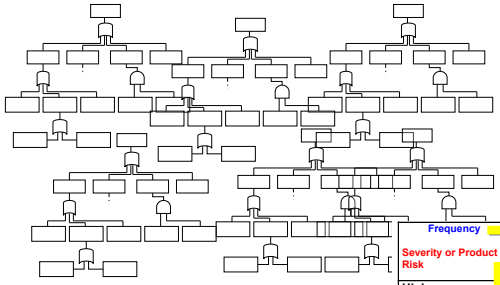
The formality of quality risk management should reflect the complexity and/or criticality of the issue to be addressed.

When should Risk Assessment be initiated ?

Event Occurs ……..	
If ……	**Then ……**
the event is judged to be insignificant or has negligible potential to impact a patient ……	do not initiate a formal risk assessment. Record the event as required by SOPs and GMP records. The reason for the decision to not to conduct a formal risk assessment is not needed.
the event may or may not be significant or may have some potential to impact a patient ……	consider moving to a formal risk assessment. Seek the advice of the QA Manager and other company management before proceeding. The reason for any decision to not to conduct a formal risk assessment is required.
the event has reasonable foreseeable potential to be significant or impact a patient ……	initiate a formal risk assessment.

Quantitative and Qualitative Risk Assessment Techniques

Quantitative Approach



A x B x C = a number

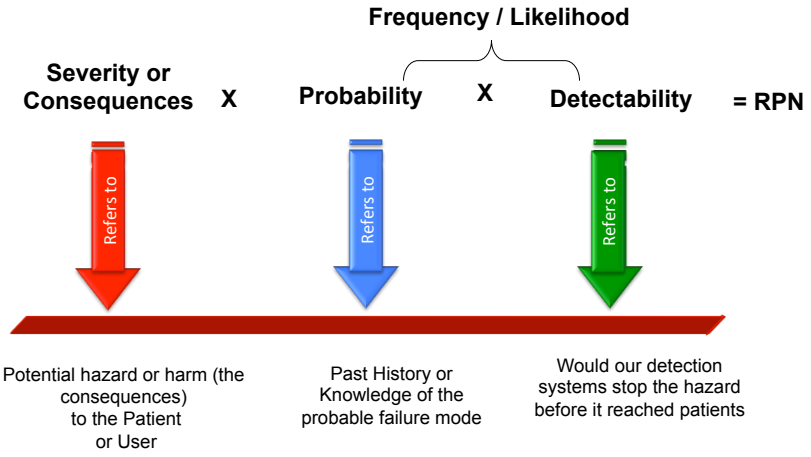
Qualitative Approach

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)



Example Hazards to Pharmaceutical Products

Purity	(Micro) Biological Hazards ○ Bacterial/viral contamination / lack of sterility assurance ○ Pyrogens ○ Bulk bioburden contamination ○ TSE/ BSE contaminants Chemical Hazards ○ API and excipient Impurities ○ Degradation products ○ Cross-contamination from other products ○ Cleaning agent residues Physical Hazards ○ Glass, metal, plastics, rubber ○ Foreign matter ○ Particulates ○ Solvents/ residues	Efficacy / Potency	Production ○ Formulation errors ○ Degradation products due to temperature ○ Contamination (see purity) ○ Lack of process validation ○ Inadequate container/closure sealing Storage ○ Shelf Life Degradation ○ Contamination ○ Expiration Distribution ○ Handling errors ○ Counterfeiting ○ Temperature exposure ○ Moisture exposure
Identity	Raw Material ○ Loss of traceability ○ Mix up, substitution or counterfeiting ○ Economically motivated contamination in the supply chain Intermediates ○ Loss of traceability ○ Mix up Finished Product ○ Incorrect labeling ○ Incorrect instructions for use ○ Incorrect shelf life ○ Incorrect Lot # or expiry date	Safety	Development ○ Bioavailability and bioequivalence ○ Clinical trials side effects Production ○ Formulation errors ○ Contamination (see purity) ○ Degradation due to inadequate handling, transport & storage Patient related ○ Foreseeable patient or clinical misuse ○ Patient compromised e.g. immuno-suppressed, aged or infant ○ Method of dosage administration ○ Incorrect medicine or dosage ○ Other medication, drugs interactions. ○ Unforeseen adverse events

Severity Analysis
Relating Hazards to Harm – Example

Potential Hazard	Foreseeable sequence of events (Failure Mode)	Hazardous situation	Harm (Severity)
Chemical (cleaning residue)	1) Incomplete cleaning of equipment used in prod'n 2) Use wrong cleaning agent	Patient receives undetected dose of impurities	• Adverse reaction • Acute injury • Complaint
Biological (Microbial contamination)	(1) Excessive bioburden in bulk mix due to: (1) poor cleaning (2) extended/ wet storage of equipment (3) Environmental	Bioburden grows through the filter and contaminates product. Lower SAL	• Fails sterility test • Bacterial infection • Death
Pyrogens (biological contamination)	(1) Excessive pyrogens in product due to: (1) HAO cycle failure (2) Inadequate vial wash	Undetected pyrogens appear in finished product.	• Fails LAL test • Febrile reaction by patient • Acute / chronic injury

WHO Suggested Severity Levels

Severity level (Quantitative)	Severity level (Qualitative)	Example description of consequences
1	**Negligible**	Will not result in harm requiring attention.
2	**Marginal**	Results in customer inconvenience and/or harm requiring local first aid treatment.
3	**Moderate**	Results in serious harm or a customer / community health problem requiring medical treatment.
4	**Critical**	Results in extensive harm or a customer / community health problem requiring hospitalisation or prolonged medical treatment.
5	**Catastrophic**	Results in death or extensive harm; a general community health problem attracting public interest and requiring significant medical treatment or hospitalisation for those effected.

WHO Suggested Likelihood/Probability Levels

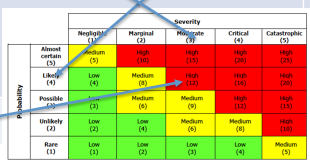
Likelihood level (Quantitative)	Likelihood level (Qualitative)	Example description of probability (based on events/time)
1	Rare	May occur every 10 – 30 years
2	Unlikely	May occur every 5-10 years
3	Possible	May occur every 1-5 years
4	Likely	May occur more than once per year
5	Almost Certain	May occur several times per year

WHO – Semi Quantitative Risk Evaluation Table (Consequences x Likelihood)

		Severity				
		Negligible (1)	Marginal (2)	Moderate (3)	Critical (4)	Catastrophic (5)
Probability	Almost certain (5)	Medium (5)	High (10)	High (15)	High (20)	High (25)
	Likely (4)	Low (4)	Medium (8)	High (12)	High (16)	High (20)
	Possible (3)	Low (3)	Medium (6)	Medium (9)	High (12)	High (15)
	Unlikely (2)	Low (2)	Low (4)	Medium (6)	Medium (8)	High (10)
	Rare (1)	Low (1)	Low (2)	Low (3)	Low (4)	Medium (5)

Risk Assessment Table - Example (Semi – Qualitative Table)

	Summarise the potential hazard	Describe the potential patient consequences of the hazard	#	Describe the failure mode that potentially causes the hazard	Describe the likelihood the failure mode could occur	#
#1	Bulk tanks used in unclean state which could result in bioburden in bulk cream mix.	Used as an antiseptic cream on open wounds – potential to infect wound and cause localized sepsis. A failure that can cause a moderate harm or adverse reaction to a patient or user but will not result in chronic harm. The harm will require treatment.	3	Bulk tank not cleaned because there is no system for a maximum dirty hold time for tanks and they are stored in wet condition. Lack of cleaning validation	A number of failures are likely to occur as the equipment lacks cleaning validation.	4
#2						



A score of 3 x 4 = 12 implies a potentially HIGH risk issue requiring mitigation

Detection Rating Scales

Rank	Detection	Criteria
1	Certain to Very High	The listed Controls have an excellent chance to almost certain to detect the Cause of Failure and/or the subsequent Failure Mode. Defect is obvious and can be kept from affecting customer. Tests are validated. 100% inspection is possible.
2	High to Reasonable	The listed Controls have a good to reasonable chance of detecting the Cause of Failure and/or the subsequent Failure Mode. Tests are validated.
3	Moderate to Uncertain	The listed Controls may, or may not detect the Cause of Failure and/or the subsequent Failure Mode. Process is manually inspected. Tests are validated.
4	Unlikely to Very unlikely	It is unlikely that the listed Controls will detect the Cause of Failure and/or the subsequent Failure Mode. Units are systematically sampled and inspected using AQL sampling. Units are manually inspected. Tests partially validated.
5	Extremely Unlikely to None	It is extremely unlikely that the listed Controls will detect the Cause of Failure and/or the subsequent Failure Mode. Occasional units are checked for defects. Control tests are not validated. Defect caused by failure is not detectable

Adding Detectability Dimension

Risk Merged with Detectability

	Risk (S x L)	Negligible	Low	Medium	High	Unacceptable
		(1)	(2 - 4)	(5 -9)	(10 -16)	(20 -25)
Detectability (D)	1	(1)	(2 - 4)	(5 -9)	(10 -16)	(20 -25)
	2	(2)	(4 - 8)	(10 -18)	(20 -32)	(40 -50)
	3	(3)	(6 -12)	(15 - 27)	(30 - 48)	60 - 75)
	4	(4)	(8 -16)	(20 - 36)	40 - 64)	(80 - 100)
	5	(5)	(10 - 20)	(25 - 45)	(50 - 80)	(100 - 125)

Risk Acceptance Criteria
RPN > 90 is an unacceptable risk - mitigation is mandatory
RPN 60 to 90 is a high risk - mitigation is mandatory
RPN 40 to 59 is a moderate risk - - mitigation is recommended but not mandatory
RPN 20 to 39 is a low risk - mitigation not required, optional
RPN < 20 is a negligible risk - mitigation not required

If detection is based on visual only and not for every batch that detectability is rated **Unlikely to Very Unlikely (4)** so the overall risk ranking score is (4x12) **48 (orange)** and therefore the requirement for mitigation is confirmed. A CAPA should be raised.

Caveats with Scoring Systems

- Scores should be the outcome of analysis/discussion;
- Can be manipulated to get desired outcomes;
- There should be a documented rationale for assigning a score;
- There is no one correct scoring tables – company must decide what is right for them;
- Scores should be defined fully in the SOP/table;
- Scoring and RPNs are a means to rank or prioritize relative risks, and **aid in** risk acceptance decisions.

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 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 one of these statements is true: (a) Both "reactive" and "predictive" risk assessment is expected by regulators. (b) Only reactive risk management is expected within the QMS (c) Predictive risk assessment as used for managing manufacturing deviations (d) Reactive risk assessment is used for assessing production processes	
3	An RPN combines Severity and Detectability	TRUE/FALSE
4	Risk Management combines Risk Assessment and Risk Control	TRUE/FALSE

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.

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.*

Qualitative RA Example

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

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 bottle from 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 bioburden or particle contamination **Harm:** Bottle could cause mild stomach infection.	3 Potential acute infection and likely will refer to Doctor	**Likelihood: No related complaints and batch near shelf-life. Passed Tests.** **Detectability: Unknown.**	2	6 **(Medium Risk)** **Action Optional**
#2	**Hazard:** Potential loss of stability due to oxidation - Toxicity of API degradent is low **Harm:** Patient may consume low potency product or degraded active.	2 In-convenience – Patient will not feel effects as self medicating.	**Likelihood: No related complaints and batch near shelf-life. Passed Tests.** **Detectability: Unknown.**	2	4 **(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.													

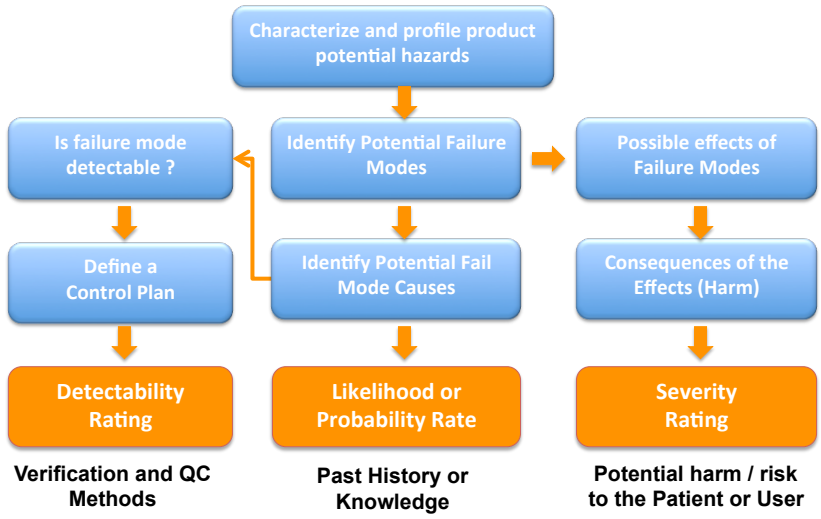
Example PHA Report (Process Step)

	Potential Risks for Current Situation							Mitigations/Controls		Revised Post Mitigation			
Process Step	Potential Risk	Consequences	Potential Causes (Likelihood of Occurrence)	Likelihood	Current Controls (Detectability)	Current Control	RPN	Recommended Mitigation Actions (Proposed Controls)	Responsible for Actions)	Consequences	Likelihood	Lack of Detect	Revised RPN**
B. Transfer of material into the chamber through the Pass Through (PT)													
B1	Tray track is not sanitary and cannot be cleaned/ sanitised effectively - location for microbial buildup therefore the sliding tray may physically transfer bioburden from the PT chamber to the isolator chamber	4	If any bioburden is resident on the slider and then detaches, or falls when slider is operated, it is unpredictable as to where the bioburden moves to. Potential for contaminant to enter the critical space (main chamber)	5	Limited detection as settle plates are not very sensitive to bioburden.	4	80	Replace the tray track system with a cleanable systems or no system at all so that base and all sides of the PT hatch can be sanitised reliably. Use sterile 6% H2O2 and 70% sterile alcohol		4	2	4	32

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 ?



FMEA Matrix Layout and Content

Step #	Step Description
1	Prepare BR
2	Clear, clean & check line
3	Set up bulk mix equipment
4	Dispense raw materials
5	Mix formulation in Vat 1

Define each successive process step from the flow chart

List here the sequential steps in the Process from the flow chart eg.
" Step 2 - Clear, Clean and Check Line"

Matrix Layout and Content

Step #	Step Description/	Potential Failure Mode
1	Prepare BR	
2	Clear, clean & check line	•Vats unclean – previous product •Etc.
3	Set up bulk mix equipment	
4	Dispense raw materials	
5	Mix formulation in Vat 1	

List the potential failure modes.
Gather information and data from existing sources and use team brainstorming, etc. to identify possible failure modes

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure
1	Prepare BR		
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contaminati on (P)
3	Set up bulk mix equipment		
4	Dispense raw materials		
5	Mix formulation in Vat 1		

Identify the effect of the potential failure. Understand how it would affect the product in terms of:
- P – Purity
- I – Identity
- E – Efficacy (strength)
- S - Safety

Example- Severity Rating Scale

Severity = likely impact of the failure

Example:

	Rating	Criteria: A failure could…	
Bad	10	Injure a customer/patient or employee	Potential Recall
	9	Be illegal	
	8	Render the product or service unfit for use	
	7	Cause extreme customer dissatisfaction	
	6	Result in partial malfunction	
	5	Cause a loss of performance likely to result in a complaint	
	4	Cause minor performance loss	
	3	Cause a minor nuisance; can be overcome with no loss	
	2	Be unnoticed; minor effect on performance	
Good	1	Be unnoticed and not affect the performance	

From: Failure Modes Effects Analysis – FMEA Methodology & Application, Gadekal Reddy
PQRI Workshop: Risk Management in Solid Dosage Form Manufacture, Jan/Feb 2005

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'
1	Prepare BR			
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contaminati on	8
3	Set up bulk mix equipment			
4	Dispense raw materials			
5	Mix formulation in Vat 1			

Score the risk according to the severity of the event – "Render the product or service unfit for use" gives a score of 8

GMP2.13 v2.07 EU FMEA

Example Occurrence Rating Scale

Example:

Rating	Time Period	Probability
10	More than once per day	> 30%
9	Once every 3–4 days	≤ 30%
8	Once per week	≤ 5%
7	Once per month	≤ 1%
6	Once every 3 months	≤ 0.03%
5	Once every 6 months	≤ 1 per 10,000
4	Once per year	≤ 6 per 100,000
3	Once every 1 – 3 years	≤ 6 per million
2	Once every 3 –6 years	≤ 3 per 10 million
1	Once every 6 –100 years	≤ 2 per billion

Bad ↓ Good

(6 sigma = 3.4 defects per million)

From: Failure Modes Effects Analysis – FMEA Methodology & Application, Gadekal Reddy
PQRI Workshop: Risk Management in Solid Dosage Form Manufacture, Jan/Feb 2005

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'	Risk 'O'
1	Prepare BR				
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contamination	8	8
3	Set up bulk mix equipment				
4	Dispense raw materials				
5	Mix formulation in Vat 1				

Score the risk according to the likelihood of the event – "Once a week" gives a score of 8

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'	Risk 'O'	Current IPC
1	Prepare BR					
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contamination (P)	8	8	Inspect vat post clean
3	Set up bulk mix equipment					
4	Dispense raw materials					
5	Mix formulation in Vat 1					

List the In-Process Control (IPC) to detect the hazard - "Inspect vat post clean"

Example Detection Rating Scale

Example:

	Rating	Definition
Bad	10	Defect caused by failure is not detectable
	9	Occasional units are checked for defects
	8	Units are systematically sampled and inspected
	7	All units are manually inspected
	6	Manual inspection with mistake-proofing modifications
	5	Process is monitored (SPC) and manually inspected
	4	SPC used with an immediate reaction to out of control conditions
	3	SPC as above with 100% inspection surrounding out of control conditions
	2	All units are automatically inspected
Good	1	Defect is obvious and can be kept from affecting customer

From: Failure Modes Effects Analysis – FMEA Methodology & Application, Gadekal Reddy
PQRI Workshop: Risk Management in Solid Dosage Form Manufacture, Jan/Feb 2005

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'	Risk 'O'	Current IPC	Risk 'D'
1	Prepare BR						
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contamination (P)	8	8	Inspect vat post clean	7
3	Set up bulk mix equipment						
4	Dispense raw materials						
5	Mix formulation in Vat 1						

Score the risk to the product according to detection rating - "All units are manually inspected" gives a score of 7

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure (PIES)	Risk 'S'	Risk 'O'	Current IPC	Risk 'D'	RPN (Score)
1	Prepare BR							
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contaminati on (P)	8	8	Inspect vat post clean	7	448
3	Set up bulk mix equipment							
4	Dispense raw materials							
5	Mix formulation in Vat 1							

Calculate Risk Priority Number (RPN) by multiplying individual risk scores together.

Classification Table for Risk Priority Number

Example:

Likelyhood \ Severity			
	200 - 400	400 - 500	> 500
	100 - 200	200 - 400	400 - 500
	<100	100 - 200	200 - 400

If RPN is high because of:
Severity – consider product redesign

Probability – investigate process control & capability

Detection – introduce mistake-proofing measures

RPN Action:

> 500	Change the design/process or implement action to reduce the RPN to a lower grouping
200 - 500	Implement Action to reduce RPN
< 200	No Action Required, may add Warning or Caution to Instructions

Matrix Layout and Content

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'	Risk 'O'	Current IPC	Risk 'D'	RPN (Score)	Action: What, Who, When
1	Prepare BR								
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contamination (P)	8	8	Inspect vat post clean	7	448	•Revalidate cleaning (QM, Feb 16) •Train all staff (Area Mgr. May 16) •Etc.
3	Set up bulk mix equipment								
4	Dispense raw materials								
5	Mix formulation in Vat 1								

List actions, responsibilities and *realistic* timescales that address the *root cause* of the failure.
Include measures as appropriate.

FMEA - Completed Matrix

Step #	Step Description	Potential Failure Mode	Effect of Failure	Risk 'S'	Risk 'O'	Current IPC	Risk 'D'	RPN (Score)	Action: What, Who, When
1	Prepare BR								
2	Clear, clean & check line	•Vats unclean – previous product •Etc.	Cross-contamination (P)	8	8	Inspect vat post clean	7	448	•Revalidate cleaning (QM, Feb 16) •Train all staff (Area Mgr. May 16) •Etc.
3	Set up bulk mix equipment								
4	Dispense raw materials								
5	Mix formulation in Vat 1								

Template Simplified FMEA Template

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:	

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

		Present Potential Risk					Remaining or Residual Risk (Post Mitigation)				
Ref	Potential Hazard/Patient Harm (Consequences) Describe Potential Failure Mode	(S)	Likelihood of Failure Mode Occurring (O)	O	RPN S x O	(S)	(O)	Final RPN S x O	Comments	Evaluation Report
#1										
#2										
#3										

EXAMPLE ONLY

Risk Control/ Risk Mitigation

1. Risk Control - Option Analysis

- What can be done to mitigate risks?
- What options are available?
- What are the trade-offs in terms of risks, benefits and costs?

2. Existing Controls

- What controls are already in place ?

3. Monitoring and Control Plans

- Can we detect the failure mode ?
- What monitoring and reporting feedback are in place ?

Risk Mitigations and Controls

- **Cannot alter severity/harm**
- Focus on the failure mode or hazard
- Focus on Likelihood/ Detectability
- Likelihood examples:
  - Validation
  - Additional Training
  - Automated Controls
  - Enhanced SOPs
- Detectability options:
  - Enhanced Sampling/Test Programs
  - Install Alarms
  - Trend analysis and alert limits

Mitigation is the implementation of measures designed to reduce the undesirable effects of a hazard.

Flash Quiz

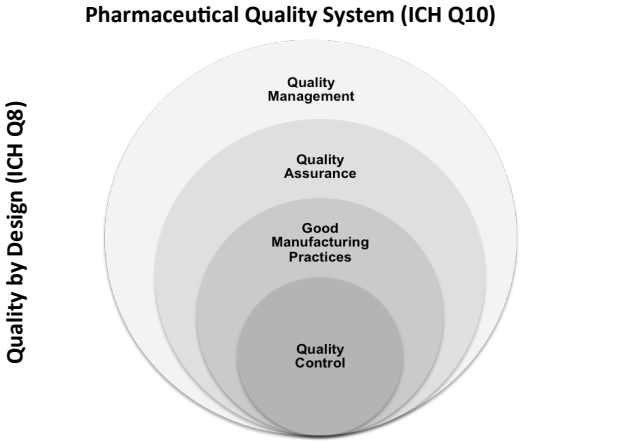
	Risk Tools	Your Selection
1	Which of these statements is true (there may be more than one) (a) FMEA is the preferred tool by regulators (b) FMEA is a more sophisticated version of PHA (c) Large numerical scales are best for FMEA (d) FMEA is good for complex processes of many steps	
2	Which of these statements is true (there may be more than one) (a) Severity can be mitigated (b) Understanding failure modes/hazards is key to good mitigations (c) It is usually better to reduce likelihood than increase detectability	
3	Only FMEA requires mitigation or controls to be documented	TRUE/FALSE
4	FMEA primarily looks at engineering and validation type studies	TRUE/FALSE

Applying Risk Assessment to Quality Events, Deviations and CAPA

ICH Q10 - Pharmaceutical Quality System

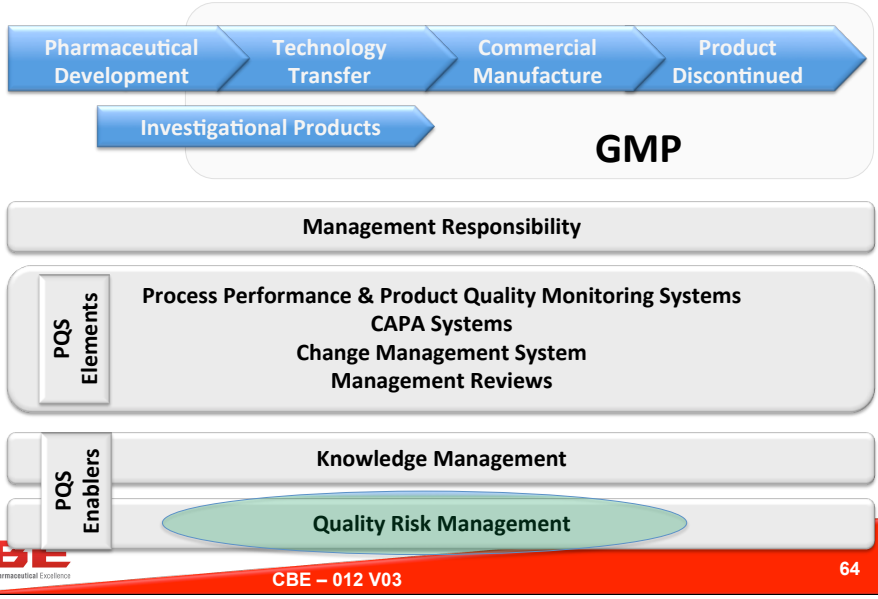
- Based on ISO 9000/ISO13485/CFR 820 systems model.
- Compliments ICH Q8 and ICH Q9.
- Applies across the product life-cycle.
- Consistent with GMPs - not intended to add new expectations to regulations and compliance.
- Applies to APIs, drug products and biotechnology.
- Strengthens the link between product development and manufacturing activities.

Pharmaceutical Quality System, Quality Assurance, GMP and Quality Control



Compliance by Design

ICH Q10 - Pharmaceutical Quality System



Integration of PQS and GMP Elements in the Quality System

PQS

- Knowledge Management, Training and Education
- Monitoring Systems
- Change Management
- CAPA & Improvement
- Management Review and Responsibility
- Quality Planning & Resources
- Process Performance and Product Quality Monitoring System

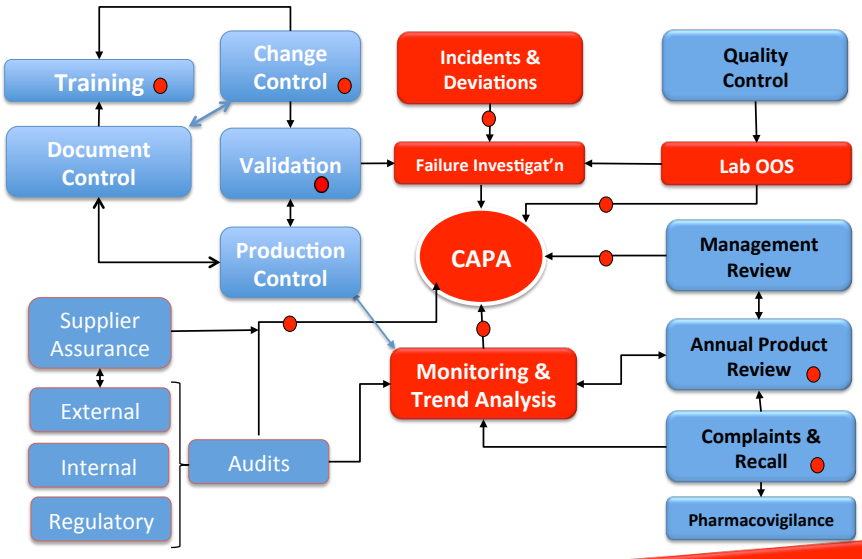
GMP

- Quality Management/ Quality Assurance System.
- Facilities and Equipment System.
- Materials System.
- Production System
- Packaging and Labeling System
- Laboratory Control System

PQS Enabler 1.6.2
Quality Risk Management (QRM)

- Quality risk management, in line with ICH Q9, provides an essential component of the Quality System.
- QRM enables both effective and efficient practices.
- Application of QRM ensures the quality system is efficient because it provides a systematic approach to escalating and prioritising significant incidents, non-compliances, trends and events for corrective and preventive action.
- FDA has emphasis on product lifecycle and risk in their QM guidance.

QRM within the PQS ?



ICH Q10 3.0 Quality System

Continual Improvement of Process Performance & Product Quality

Lifecycle goals

- Pharmaceutical development should follow principles of ICH Q8:
  - **Process Understanding**: Expert knowledge gained through manufacture or development and scale-up activities. This stage enables the understanding of CPPs and CQAs as well as worst case conditions
  - **Process Performance Qualification PPQ:** The process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
  - **Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.
- These attributes will also provide the foundation of technology transfer activities and the basis for ongoing manufacturing.

ICH Q10 3.2 Quality System Elements

- **Process performance and product quality monitoring system**:
  - Well defined systems
    - Process control CPV
    - Identification of improvement areas
- **Corrective action and preventive action (CAPA) system**
  - In place and effectiveness evaluated
- **Change management system**:
  - In place
  - QA oversight
  - Utilizes science and ***risk-based assessment***
- **Management review of process performance and product quality**
  - Structured
  - Supports continual improvement

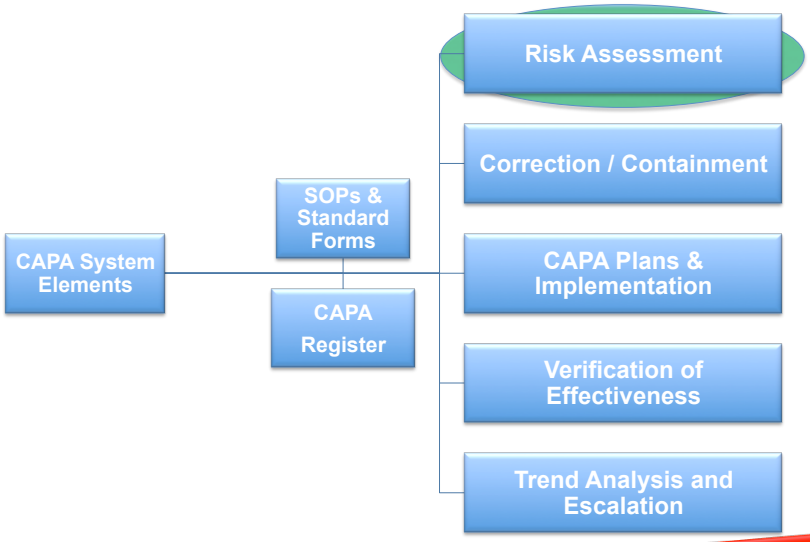
ICH Q10 3.2.1 - Process Performance & Product Monitoring

- **"An effective monitoring system provides assurance of the continued capability of processes and controls to meet product quality"**
- Recommended elements:
  - Use ***risk management***
  - Provide **tools** for measurement
  - **Verify** continued operation within a **state of control**
  - Identify sources of **variation** - potential for improvement
  - Include feedback and structured management reviews.
  - Opportunities to increase knowledge of "design space"

ICH Q10 3.2.2 - Corrective and Preventive Action

- Should have a system for implementing CAPA 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

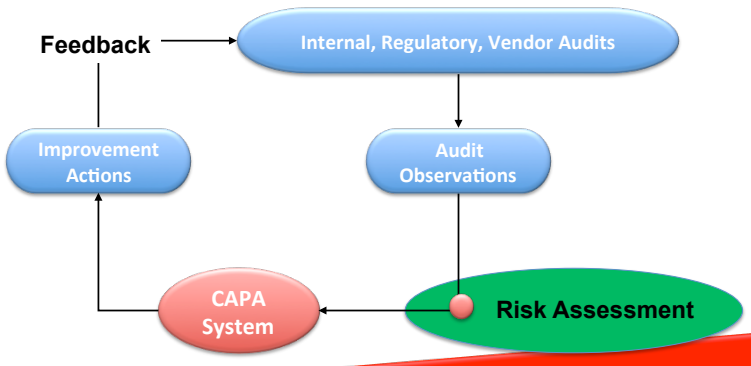


"Linkage" of the QMS system elements

- Each of the major elements are **inter - linked** to other elements
- Elements either drive or feed others or vice versa
- Linkage of related elements is critical to quality management oversight
  - Without strong linkage, identification of problem root cause is difficult
  - With linkages, problems and root causes can be traced through the linked system
- Linkage enables "escalation" of significant issues
- E-QMS systems greatly assist this process

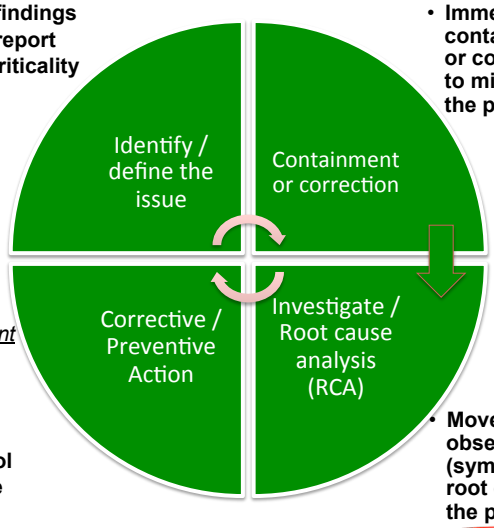
Example of Direct Linkage (CAPA and Audits)

- Audits are a "driver" to generate CAPAs
- CAPA activity improves compliance
- Improved compliance reduces audit observations



CAPA Processes

- Audit findings
- Audit report
- Rate criticality



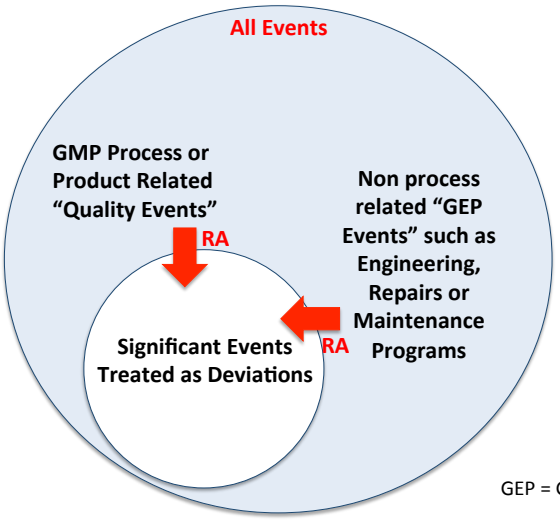
- Immediate containment or correction to minimise the problem

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

- *Risk Assessment*
- Permanent fix of the problem
- Prevention of recurrence
- Change Control
- Verify effective

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

Assessing Quality Events and Deviations



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

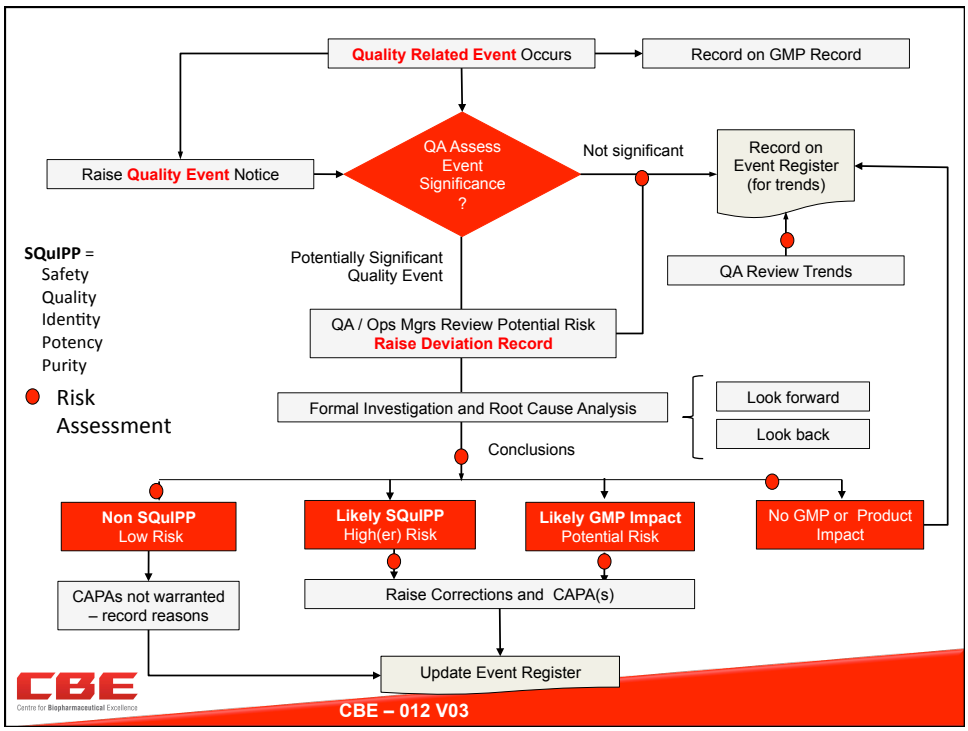
GEP = Good Engineering Practice

Deviation System Key Elements

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).

SQuIPP=Safety, Quality, Identity, Purity, Potency



Flash Quiz

	Risk Assessment	Your Selection
1	Which one of these statements is NOT correct: (a) Applying risk management is mandatory as the 1st step in deviation investigation. (b) The level of risk management should be commensurate with patient risk. (c) Risk assessments should be documented in some way per GMPs. (d) GMP requires us to conduct only reactive risk assessments	
2	Which of these statements is most correct (a) Risk assessment is applied to proposed major change controls (b) Risk assessment is applied to all proposed change controls (c) Risk assessment is only required when assessing serious/significant customer complaints (d) Risk assessment is not required when conducting qualification of new GMP equipment	
3	Hazards and Patient Harms are directly linked	TRUE/FALSE
4	Probability of Occurrence and Detectability are indirectly linked	TRUE/FALSE

What Does PICs Say ?

- 1.2 vi. records are made, manually and/or by recording instruments, during manufacture which demonstrate that all the steps required by the defined procedures and instructions were in fact taken and that the quantity and quality of the product was as expected. **Any significant deviations are fully recorded and investigated;**
- 1.4 (PQR) A review of all **significant** deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken.
- **Batches should not be released before deviations are investigated and resolved.**

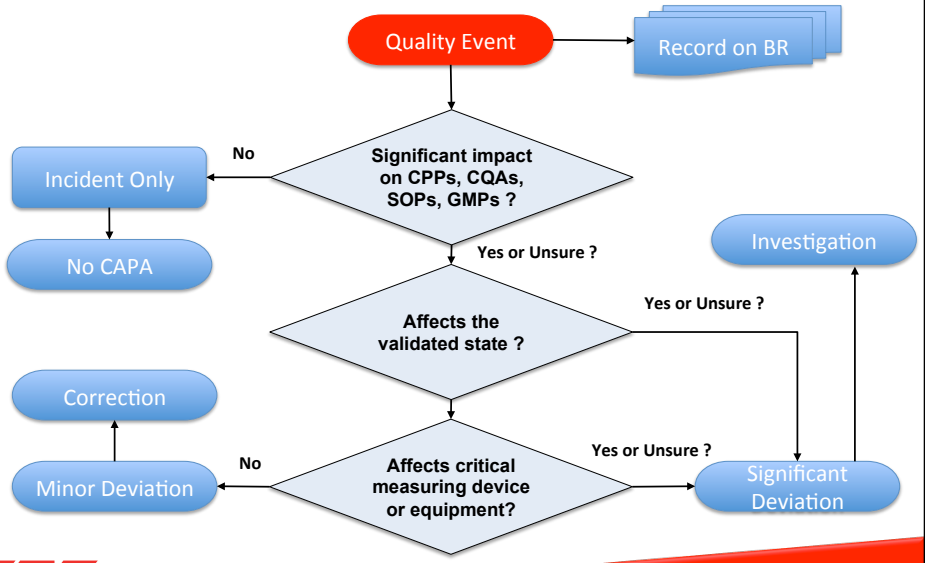
What Does PICs Say ?

- 5.15. ….. If a deviation occur, it should be approved in writing by a competent person, with the involvement of the Quality Control Department when appropriate.
- 5.39. Any significant deviation from the expected yield should be recorded and investigated.
- 6.30 ….. a stability study should be conducted after any significant change or significant deviation to the process or package.

How to separate minor events from "significant" events ? - Options

- Production can independently decide what is or is not an event (all events should be recorded on the batch record) and QA can review at the time of review of the record;
- Production can send all events up to QA for their review via a notice;
- Can be an informal/unrecorded discussion between Production and QA;
- Can be a formal/recorded discussion between Production and QA;
- Can use a simple form as a decision check-sheet to "qualify" an event as a deviation.

Using a Decision Tree To Risk Assess Events and Deviations



Risk Assess a Quality Event Using a Check Sheet

2. Preliminary Risk Assessment (Formal Assessment of potentially significant event)

Consider the following questions to assess the potential product risks (SQuIPP impact) - Safety, Quality, Identity, Potency, Purity)

1	Likely the event could impact Sterility Assurance, bioburden or endotoxin ?	☐ 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 cause defects in container closure integrity ?	☐ Yes ☐ No ☐ Unsure ?
7	Likely the event could affect product quality or stability in the marketplace ?	☐ Yes ☐ No ☐ Unsure ?
8	Is the event related to a GMP non-conformance or outside the "validated state" ?	☐ Yes ☐ No ☐ Unsure ?

Other considerations

9	Could this event impact batches already released to the marketplace ?	☐ Yes ☐ No ☐ Unsure ?
10	Could this event impact SQuIPP for future batches if not corrected ?	☐ Yes ☐ No ☐ Unsure ?
11	Is this event part of a trend ? (Review the Deviation / Quality Event Trend register)	☐ Yes ☐ No ☐ Unsure ?
12	Does this event impact a CPP or a CQA ?	☐ Yes ☐ No ☐ Unsure ?

Example of Checksheet for Initial 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)

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 from a 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

Change Management and Risk Assessment

ICH Q10 3.2.3 – Change Management

Should include:

- An assessment according to risk using the QRM system
- A review of changes against marketing authorisations (product registration)
- Proposed changes should be evaluated by expert teams from relevant areas (e.g., Pharmaceutical Development, Manufacturing, Quality, Regulatory Affairs and Medical), to ensure the change is technically justified. Prospective evaluation criteria for a proposed change should be set;
- After implementation, a review of the change should be undertaken to confirm the change objectives were achieved and that there was no negative impact on product quality.

Possible Change Control Levels

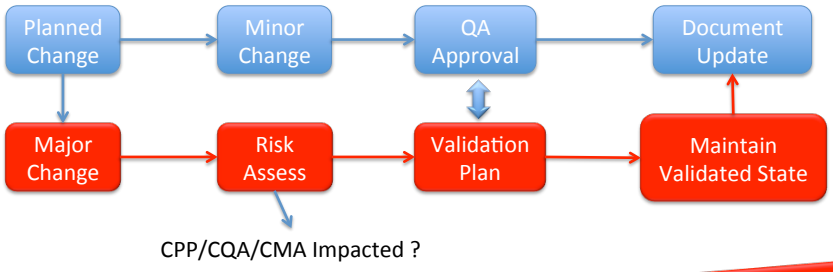
Minor Change
The change is unlikely to have a detectable impact on critical attributes of the product or process. Change is procedural or editorial in nature only.

Moderate Change
The change could or may have a significant impact on critical attributes of the product or process.

Major Change
Change is likely to or will have a significant impact on critical attributes of the product or process.

Change and Risk Assessment

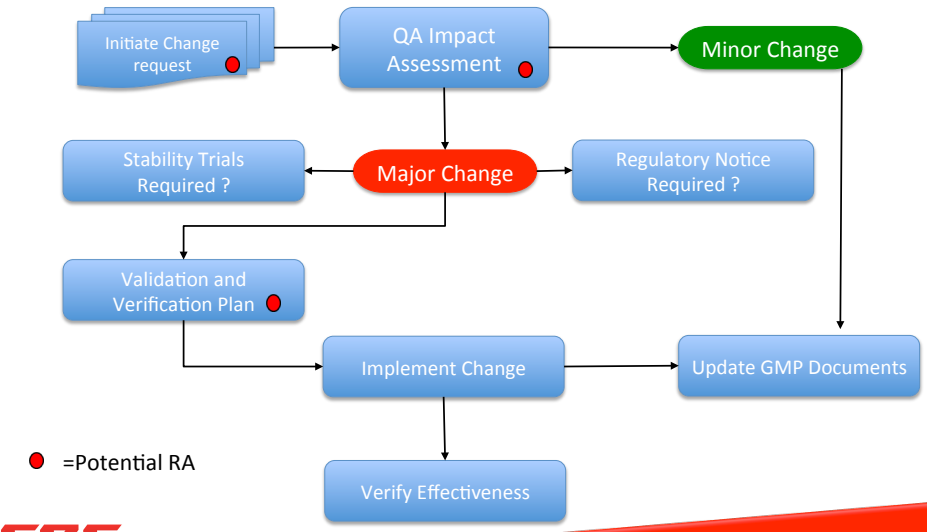
- Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the **impact** on the validated status or control strategy assessed. (EU cGMP – Annex 15)
- The likely impact of the change of facilities, systems and equipment on the product should be evaluated, **including risk analysis**.
- ***The need for, and the extent of, requalification and re-validation should be determined.***



Types of Change

- **Permanent**
- **Temporary** (Temporary for a Lot (batches impacted) or Temporary for Date (Time period of temporary change))
- When a temporary change affects a specific lot(s), a true copy of change record must form part of the completed batch record for each affected lot(s).
- GxP relevant changes include any change to the validated state of equipment, facility, product, process, utility, automation system, IT system, material or quality system.

Change Control Impact Assessment



Classifying as Minor or Major Change

If	Then .....
the change is judged to be minor or has negligible potential to impact a patient……	do not initiate a risk assessment. Record the change as required by this SOP.
the change is judged to be major but does not involved a significant change to a CQA or a CPP and in not complex in nature …….	a formal documented risk assessment is optional and change control can be documented as part of impact assessment.
the event has reasonable foreseeable potential to be significant or impact a patient **or** involves a significant change to a CQA or CPP **and/or** is complex in nature	a formal (documented) risk assessment is generally warranted. If it is decided that a formal risk assessment is not required the reasons for this should be documented on the change record.

Examples of Minor and Major Changes

Changes to		Minor	Major
Contract Service Providers			✓
Regulatory Updates eg. Pharmacopeial update		✓	✓
Contract Testing laboratories		✓	✓
Contract Manufacturers			✓
Critical Equipment or Services	•"like for like" •Different	✓	 ✓
Master Engineering Diagrams / schematics etc.			✓
Change to a Critical Quality Attribute (CQA)		Tighten	Widen
Change to a Critical Process Parameter (CPP)		Tighten	Widen
Change to a Critical Starting Material Atrribute (CSM)		Tighten	Widen
Master Batch Records (validated processes and Formulation)			✓
Specifications Components	Primary – registered Secondary & non registered	 ✓	✓
Packaging Materials	Primary – registered Secondary & non registered	 ✓	✓ ✓
Printed Matter	Primary – registered Secondary & non registered	 ✓	✓ ✓
Product - Specification	Tighten the Limit Widen the Limit	✓	 ✓
Product - Test	Add a Test Delete a Test	✓	 ✓
Shelf Life Conditions (expiry or storage)			✓
Test Methods		✓	✓
Utilities or Services	Critical Non-critical	 ✓	✓

Flash Quiz

	Change Management	Your Selection
1	Which of these statements is true (there may be more than one) (a) Changes can be Minor or Major in nature (b) Assessing change impact is the role of the Production Manager (c) Stability Trials are needed for Minor Changes (d) Changes to CPPs or CQAs generally indicate a Major impact	
2	Which of these statements is true (there may be more than one) (a) "Like for like" equipment changes are generally Minor impact (b) Temporary changes should be classified as Deviations (c) Validation and Verification Plans are required for Major changes (d) Minor changes require effectiveness verification	
3	A change to a critical process parameter (CPP) require Validation and Verification	TRUE/FALSE
4	A change to product specification can be either minor or major impact	TRUE/FALSE

Applying QRM to Computerised Systems

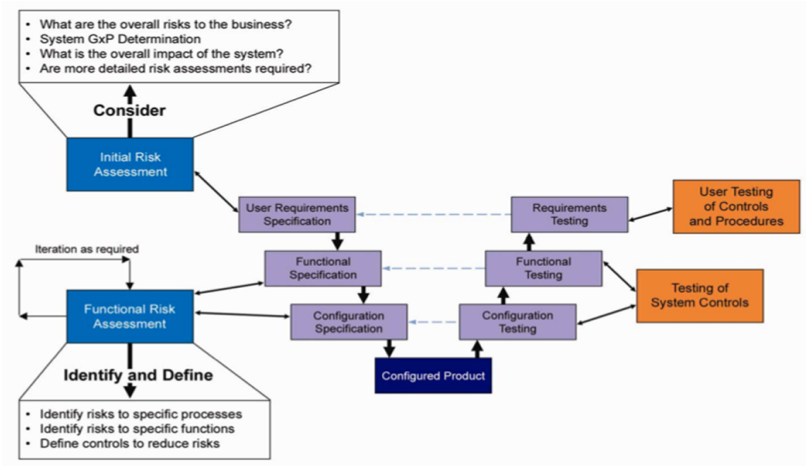
Some Useful Reference Documents

- ICH Q10 - Pharmaceutical Quality System
- ICH Q8 – Pharmaceutical Product Development
- ICH Q9 - Risk Management in Pharmaceuticals
- Current PIC/S Code of Good Manufacturing Practice for Medicinal Products including Annex 11 Computerised Systems
- PIC/S PI-011-3 – Good Practices for Computerised Systems in Regulated GxP Environments
- Good Automated Manufacturing Practice (GAMP) 5.0
- WHO Guideline for the Manufacture of Pharmaceutical Products

Computer Systems RA Approach

- All systems determined to be GxP related are evaluated for their compliance to the applicable codes of GMP, especially Annex 11 of the PIC/S Code of Good Manufacturing Practice for Medicinal Products.
- The validation RA is undertaken to determine the appropriate level of validation relevant to the system in question.
- The RA is made with reference to the GAMP V categories of criticality and complexity.

GAMP 5 V model



Review of GAMP Levels

Category 0 is included to recognise that operating systems may impact related software and therefore requires a level of control.

Category	Description	Examples	Typical Approach
Category 2 (old GAMP 4 Category 2) Firmware, HMIs and Controllers	This category is essentially hardware with embedded firmware such as PLCs, EPROMs or computer human interface/control panel (HMIs) etc. that cannot be programmed by users but can typically be configured from a series of limited options. Note: Under GAMP 5 this category is removed but has been included here for completeness.		As a policy all firmware is qualified as a controller integral to the associated equipment. Equipment IQ documentation needs to reference FW versions and configuration settings. No URS and IQ only required.

Category	Description	Examples	Typical Approach
Category 1 Infrastructure Software **Operating Systems (Compilers and System Configuration Files)**	• Operating Systems • Database Engines • Statistical packages • Spreadsheets (the program itself) • Scheduling tools • Version control tools layered software (i.e., upon which applications are built) • Software used to manage the operating environment	• Operating systems include OS/400, UNIX, VMS, MS Windows NT, MS Windows 8 and MS DOS, which may run on mainframe, mid-range, server and client PC computers	Specific validation of commercial software which is established in the market is not required however records of operating systems and their versions shall be maintained in the computer systems validation register or within the IT department. If a new version of an operating system is required, a review should be conducted to determine the possible impact of the new operating system on the existing software application(s), and system configuration files • Record version number, verify correct installation by following approved installation procedures • See the *GAMP Good Practice Guide: IT Infrastructure Control and Compliance*

Category	Description	Examples	Typical Approach
Category 3 Non- Configured	Off the shelf products that cannot be changed to match business processes Run-time parameters may be entered and stored, but the software cannot be configured to suit the business process	• Commercial Off-the-Shelf (COTS) software • Instruments (See the *GAMP Good Practice Guide: Validation of Laboratory Computerized Systems* for further guidance)	• Abbreviated life cycle approach • URS • Risk-based approach to supplier assessment • Record version number, verify correct installation • Risk-based tests against requirements as dictated by use (for simple systems regular calibration may substitute for testing) • Procedures in place for maintaining compliance and fitness for intended use

Category	Description	Examples	Typical Approach
Category 4 Configured	Configured products provide standard interfaces and functions that enable configuration of the application to meet user specifications. Software, often very complex, that can be configured by the user to meet the specific needs of the user's business process. Software code is not altered	• LIMS • ERP • MRPII • Building Management Systems • Spreadsheets (standard functions) Note: specific examples of the above system types may contain substantial custom elements	• Life cycle approach • Risk-based approach to supplier assessment • Demonstrate supplier has adequate QMS • Some life cycle documentation retained only by supplier (e.g., Design Specifications) • Record version number, verify correct installation • Risk-based testing to demonstrate application works as designed within the business process • Procedures in place for maintaining compliance and fitness for intended use • Procedures in place for managing data
Category 5 Custom or Bespoke	Applications developed to meet the specific needs of the regulated company. Software custom designed and coded to suit the business process	Varies, but includes: • Internally and externally developed IT applications • Internally and externally developed process control applications • Custom firmware • Spreadsheets (macros and code)	Same as for configurable, plus: • More rigorous supplier assessment, with possible supplier audit • Possession of full life cycle documentation (Functional Specifications, Design Specifications, structural testing, etc.) • Design and source code review

Risk Categorisation

- Depending upon the criticality and complexity of the system eg. the ERP system, a separate Validation Plan may be required, or a set of Validation Protocols (IQ/OQ/PQ) may be more applicable.
- Most computer systems consist of components of differing GAMP categories and therefore different systems, or components, may require different levels of validation.
- The software component of a GxP related computerised system is generally considered to be a relatively high(er) risk.
- This relative risk increases with increasing system complexity (number of functions, number of interfaces with other computer systems, concurrent users and processes etc) and increasing degree of customisation (e.g. amount of bespoke source code and functions).
- It is good policy to create as site CVMP

Initial Risk Assessment

Initial risk assessments for computer systems are generally based on:

- **Criticality:** to Product Quality and GMP compliance.
- **Complexity:** how complex the system is. There is a relationship between the complexity of the software and its likelihood of failure. The more complex the system the more likely it is to contain programming errors and therefore more likely to fail. The is often indicated by the Category of the software

Criticality Severity / Impact on Product and GMP Compliance (if a fault occurred)		**Complexity** Likelihood of Occurrence of a Fault		
		Low Category 1/2	**Medium Category 3/4**	**High Category 4/5**
	High			
	Medium			
	Low			

	Extensive validation is expected. URS required, Full V model applicable
	Validation via V model. Application risk based. Verification testing expected
	No validation, limited verification expected. V model is not expected.

Computerised GxP System - Risk Assessment Form

Software Description:	**Risk Assessment #** **CSV RA .....**
Software Number/Ver	
GAMP Level: * 1/ 2 / 3 / 4 or 5	**Reviewer:**
Assessment Scope / Assumptions Made	

Use this table for each computerized system function/sub-function assessed

Function Description		**Sub-Function Description**		
	Risk Scenario - (what could go wrong)	**Criticality (Severity)**	**Complexity (likelihood)**	**Risk Classification**
1				
2				
3				

Risk Assessment Approved by: (System Owner): ..... Date: .....
Risk Assessment Approved by: (Quality Assurance): ..... Date: .....

FRM-SOP-VAL-XXX
Equipment Impact Assessment Checklist

Item Name:	Equipment #:
Part of Process Line:	Location/Room:
GxPs taken into account: ☐ GMP ☐ GDP ☐ G(QC)LP ☐ GAMP ☐ Other	
Description of the main functions:	

Impact Assessment Checklist

	Complete the checklist questions below by ticking each line. If the answer is Yes but only related to a component of the item tick Yes and the Component box.	Component	Yes	No
1	Is the item, or components in direct contact with the product or auxiliary solutions during production or during monitoring ?	☐	☐	☐
2	Item provides an excipient or process ingredient?	☐	☐	☐
3	Does the item (or a component) produce data which impacts in process or final product release?	☐	☐	☐
4	Does the item wholly or partly independently decide on the further processing of products?	☐	☐	☐
5	Does the item (or a component) monitor a CPP or WPP control system with no independent verification?	☐	☐	☐
6	Item preserves product quality e.g. vent filter, HVAC, Gas etc.?	☐	☐	☐
7	Failure or alarm has direct effect on product quality or impacts a CPP/WPP?	☐	☐	☐
8	Does the item directly or indirectly control/monitor prescribed environmental conditions of products?	☐	☐	☐
9	Is the item involved in the generation / processing of analysis values?	☐	☐	☐
10	Does the item permanently save "critical" data?	☐	☐	☐
11	Does the item use electronic records / electronic signatures?	☐	☐	☐
12	Does the time contain data that describes the product or product quality?	☐	☐	☐
13	Does the item contain data (paper, files) that are used for registration with agencies?	☐	☐	☐
14	Is the item used as a primary or supporting source for batch tracing?	☐	☐	☐
15	Does the item directly or indirectly control/monitor the storage of products in regard to packaging, temperature, RH% or storage duration?	☐	☐	☐
16	Does the item automatically provide medically relevant information?	☐	☐	☐
17	Are products labeled with the item?	☐	☐	☐
18	Is item used for cleaning/sanitation or product contact equipment or sterilization?	☐	☐	☐

Opinion of a Subject Matter Expert (if in doubt)	
	Sign
	Date

Opinion of a Subject Matter Expert (if in doubt)	
	Sign
	Date

Classification

☐	DIRECT IMPACT	If the answer to any one of the above is Yes then the item is **Direct impact.**
☐	INDIRECT IMPACT	If the answer to any one of the above is Yes but relates to a component only then the item is **Indirect Impact.**
☐	NO IMPACT	If the answer to all of the above is No then the item is has **no (GxP) impact.** This conclusion does not imply that it does not have GEP significance.

Complexity Assessment

Classify the item as:

☐	COMPLEX	**Complex** equates to novel or multi-module equipment where there is a need for integrated components to work synchronously e.g. a freeze dryer or filling machine
☐	NOVEL	A novel item is one that is custom built for the process step – it may be either complex or simple, but is generally classified as complex.
☐	SIMPLE	**Simple** equates to equipment that has only one module or unit e.g. a filter press, a mixing tank or an incubation room. These items are often purchased "off the shelf" are stand alone and not integrated

Conclusion:

Provide a concise justification for the classification of the item addressing both criticality and complexity.

Approval of Report:

Name/Title	Signature	Date
Engineering		
Production		
Quality Assurance		

Quality Risk Management and Computer Systems- Data Integrity Concerns

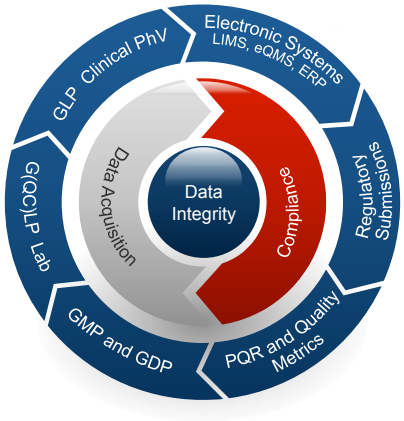
USD $16billion later…….

Data Integrity Scope

Quality Culture

"Quality culture is the collection of values, beliefs, thinking, and behaviours …... that contribute to creating a quality culture to assure data integrity."

PICs Guidance – Good Practices for Data Management and integrity in regulated GMP/GDP environments.



Governance

"Data governance systems should be integral to the pharmaceutical quality system described in PIC/S GMP/GDP."

PICs Guidance – Good Practices for Data Management and integrity in regulated GMP/GDP environments

Current Information Landscape

- Cloud, Sharepoint, SAS, data mining, Facebook, Skype, Linkedin, email, Instagram, Twitter, Snapchat, Tinder, Dropbox, pdf, …..... and Paper.
- LIMs, eQMS, PhV databases, ERP/MRP, eCTD submissions, Documentum, Lab. Data Acquisition Systems, statistical analysis tools etc….. and Paper.
- The way in which regulatory data is generated, stored and transmitted is rapidly evolving in line with ongoing development of software technologies, supply chains and outsourcing.
- Data Integrity however continues to be a basic regulatory requirement.

What is Data Integrity?

MHRA / PICs:

- *The extent to which all data are complete, consistent, and accurate throughout the data lifecycle*.*

- From initial data generation and recording through processing (including transformation or migration), use, retention, archiving, retrieval and destruction.

(**Note the lifecycle approach is consistent with the principles of ICH Q10 Pharmaceutical Quality Systems*)

Key Data Integrity Attributes – ALCOA+

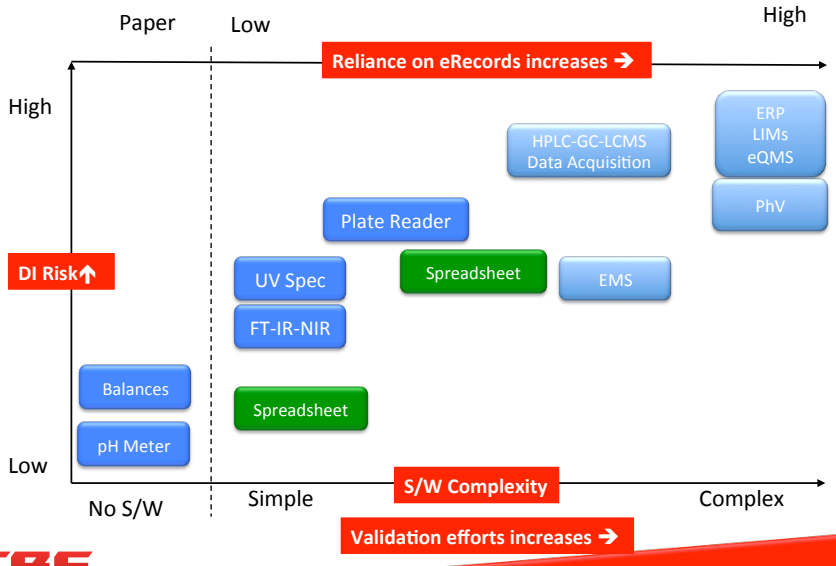
Attributable	Legible	Contemporaneous	Original	Accurate
• Who actually acquired the data or performed the actions and when? • Signed and dated	• The data must be legible / readable. • The record should be permanent • The record should be enduring and be on proven storage media	• Data must be recorded in real time as and when it occurred. • Should be carried out in close proximity to its occurrence.	• Data must be preserved in its unaltered state. • If raw data is not kept there must be solid documented justification. • The records should not have been tampered with.	• Data must correctly reflect the measurement or observation • There should be no omissions.

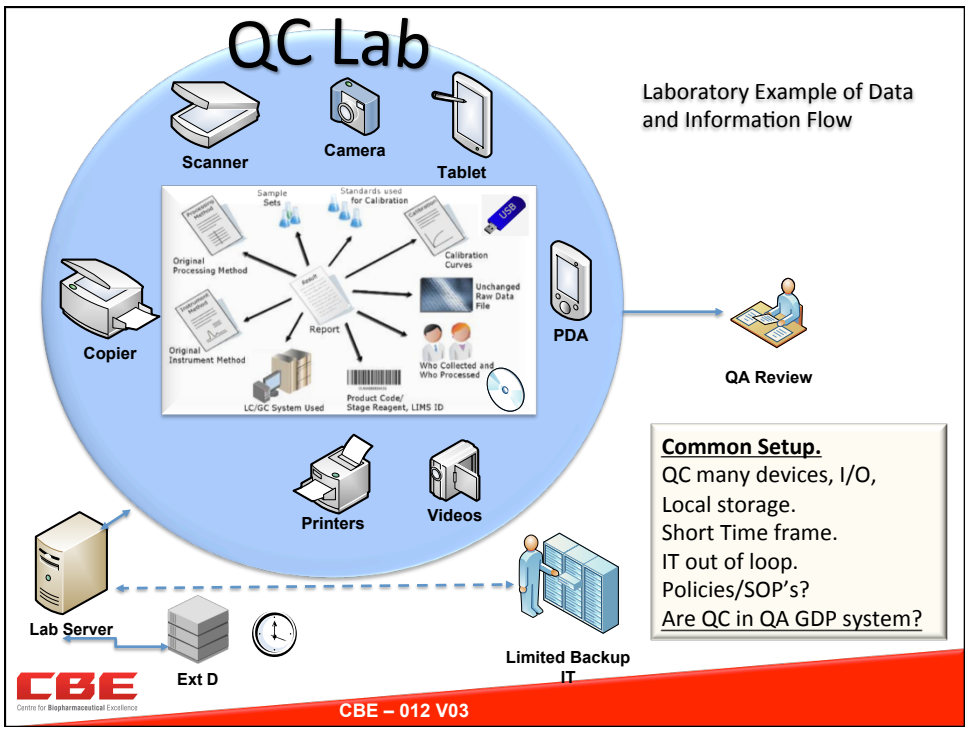
+ adds Complete, Consistent, Enduring and Available

Data Criticality and Risk

- Which decisions does the data influence ?
- What is the impact of the data to product quality and safety ?
- Vulnerability of the data to alteration (involuntary or deliberate) ?
- Degree of manual interfaces needed ?

DI Risks Associated with GxP Related Electronic Systems





WHO-TRS996- Annex 5*

A good practical guide, aligned with PIC's;

- Uses as THE starting point, the ALCOA principles put forward in DI guidelines.
- Uses the concepts of;
  - Good Documentation Practice **GDocP** and;
  - Good Data and Record Management Practice's **GDRP** throughout.
- Covers traditional, hybrid and electronic environments.
- Provides good case studies and examples.

*http://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf

GDocP and GDRP

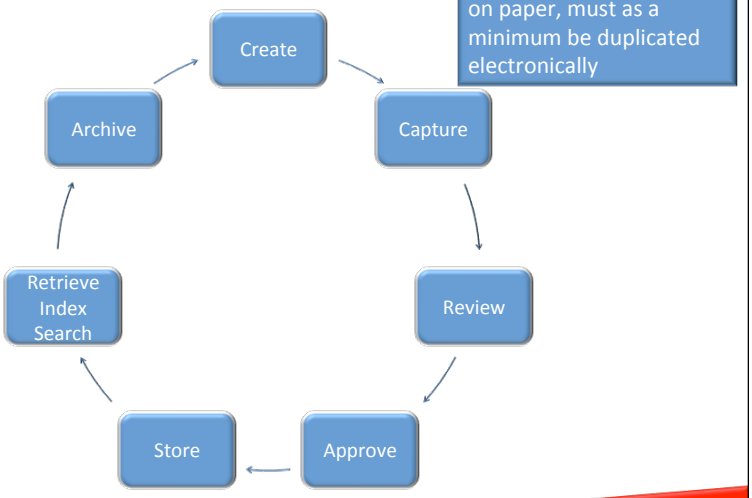
- **GDocP refers to:**
  - *"Good documentation practices, are those measures that collectively and individually ensure documentation, whether paper or electronic, is secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate."*
- **GDRP (Good Data and Record management Practice) refers to:**
  - *"The totality of organized measures, that should be in place to collectively and individually ensure, that data and records are secure, attributable, legible, traceable, permanent, contemporaneously recorded, original and accurate, and that if not robustly implemented, can impact on data reliability and completeness, and undermine the robustness of decision-making based upon those data records."*

WHO_TRS_996_annex05

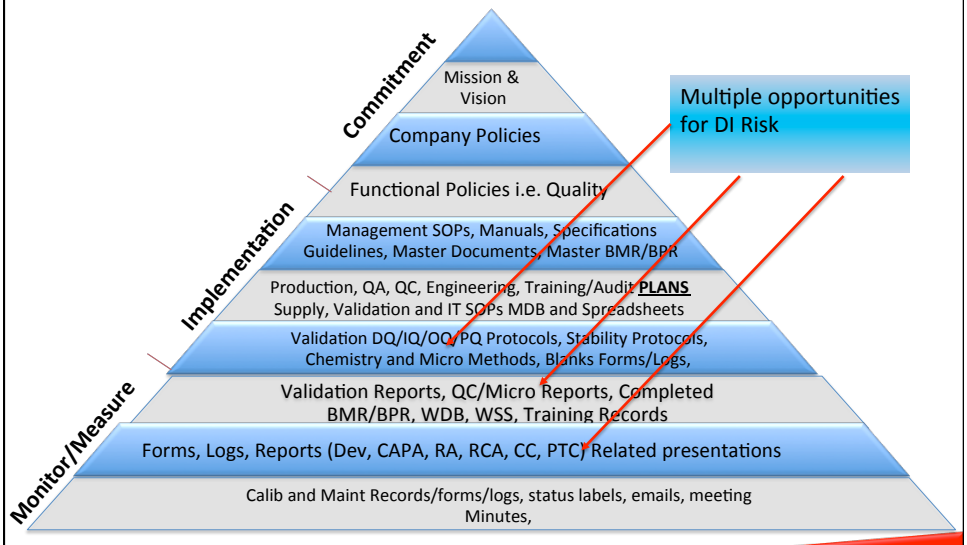
The Technology Context

- The regulatory authorities worldwide have had an increasing concern over the reliability of **GDocP** and **GDRP,** due to the rise in issues directly related to the **lack of risk management**.
- Technology has evolved over the years, without companies improving the detection of situations, where data reliability could be compromised, and/or, to investigate and address root causes when failures do arise.
- GMP organisations have been using CSV now for many decades, but have failed to adequately review and manage original electronic records and **instead often only review and manage incomplete, and/or inappropriate printouts.**

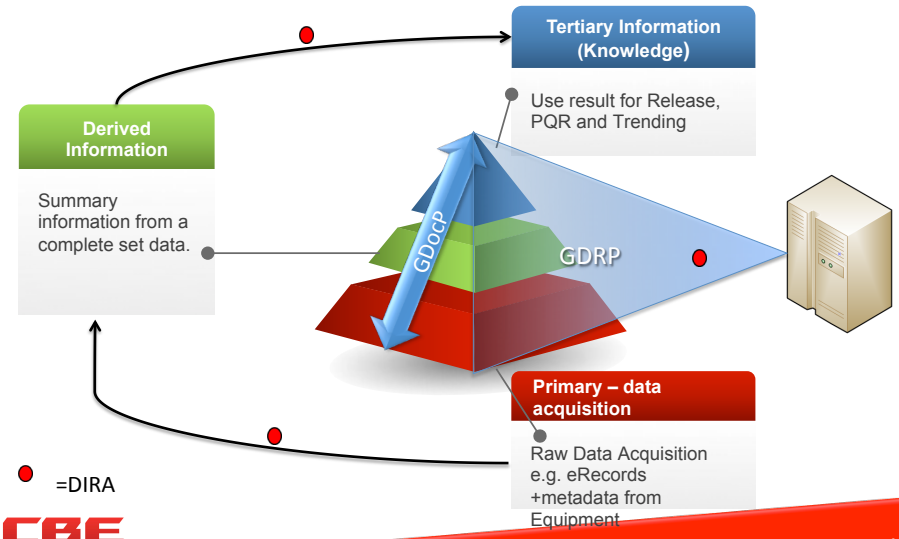
Information Lifecycle



Documentation Hierarchy

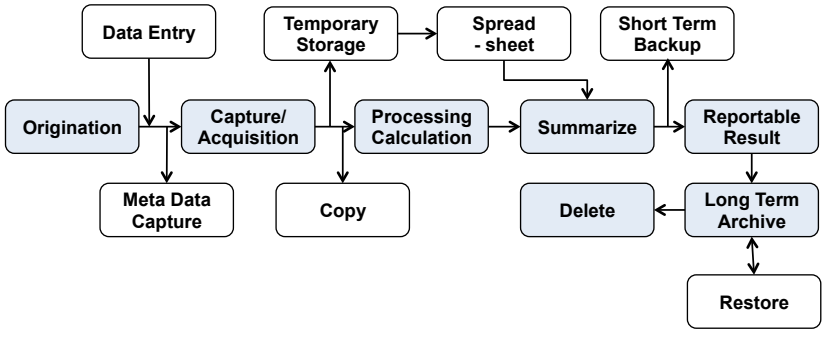


How GDP/GDRP and Data Integrity Interact



Assessing Risk of DI Vulnerability

1. Map data lifecycle in a flowchart

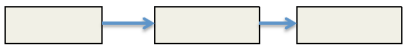


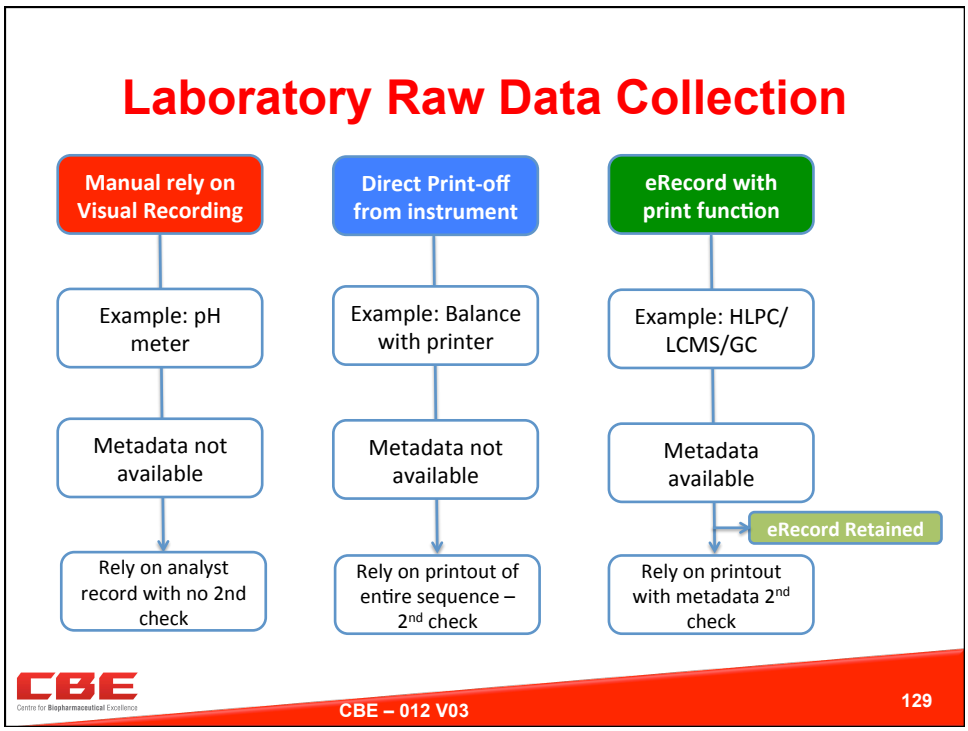
2. Analyse each step for DI vulnerability or risk

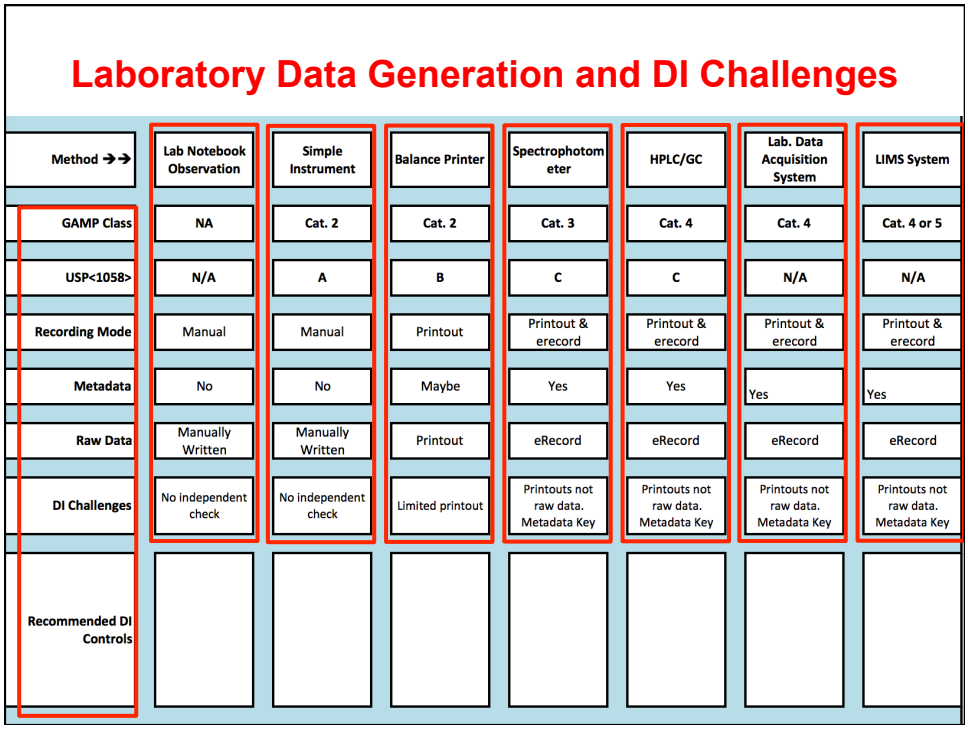
Mapping Process Vulnerabilities

Process Step	Initiate →	Acquire →	Process →	Calculate →	Report →	Archive
Where from/to ? Storage media						
MetaData / Audit Trail						
Human Access Manipulation						
Calculations Summaries						
Security Level Static/Dynamic						
Other Information						

Understanding Vulnerability- Checksheet

Vulnerability Assessment Checklist				
	Describe the Data Flow Process Step(s). 	Risk		
		High	Medium	Low
1	Does the data originate from a validated source / instrument / equipment ?	□	□	□
2	Is the data stored permanently (becomes static) ?	□	□	□
3	Is the original data and meta data etc. captured in static form at these steps ?			
4	Is there metadata / audit trail associated with the data ? How extensive ?	□	□	□
5	Is the metadata / audit trail captured and protected from change ?	□	□	□
6	Is the data captured by a human ? or machine/instrument ?	□	□	□
7	How is the data passed between sequential process steps ?	□	□	□
8	Is the data available for alteration/change during transfer ?	□	□	□
9	In which process step/system is the data processed ? is this step validated ?	□	□	□
10	Are the established password access controls to protect the data ?	□	□	□
11	Is the data transformed or migrated at this step ?	□	□	□
12	Is there analogue to digital conversion of the data at these steps ?	□	□	□
13	Is there a human data entry step ? Is there a double check in accuracy of entry ?	□	□	□
14	Can the data be modified at this step ? if so is it audit trailed ? Password access ?	□	□	□
15	Is there data editing required ?	□	□	□
16	Is the data calculation / summary step manual or automated ? double checked ?	□	□	□
17	Can the data be electronically copied and exported ? Can it be deleted ?	□	□	□
18	Other considerations ?	□	□	□


Laboratory Raw Data Collection
Manual rely on Visual Recording
Example: pH meter
Metadata not available
Rely on analyst record with no 2nd check
Direct Print-off from instrument
Example: Balance with printer
Metadata not available
Rely on printout of entire sequence – 2nd check
eRecord with print function
Example: HLPC/ LCMS/GC
Metadata available
eRecord Retained
Rely on printout with metadata 2nd check
CBE – 012 V03
129


Laboratory Data Generation and DI Challenges
Method →→
Lab Notebook Observation
Simple Instrument
Balance Printer
Spectrophotometer
HPLC/GC
Lab. Data Acquisition System
LIMS System
GAMP Class
NA
Cat. 2
Cat. 2
Cat. 3
Cat. 4
Cat. 4
Cat. 4 or 5
USP<1058>
N/A
A
B
C
C
N/A
N/A
Recording Mode
Manual
Manual
Printout
Printout & erecord
Printout & erecord
Printout & erecord
Printout & erecord
Metadata
No
No
Maybe
Yes
Yes
Yes
Yes
Raw Data
Manually Written
Manually Written
Printout
eRecord
eRecord
eRecord
eRecord
DI Challenges
No independent check
No independent check
Limited printout
Printouts not raw data. Metadata Key
Printouts not raw data. Metadata Key
Printouts not raw data. Metadata Key
Printouts not raw data. Metadata Key
Recommended DI Controls

Application of Risk Assessment to PV of Bulk Antigen