Quality Risk Management

DCVMN regional Workshop Sao Paulo, November 24-28th

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Agenda

- ICH Q9 and ICH Q10 : what is expected?
- Tools in risk analysis
- Building a probability, severity, detectability table
- Practical Exercises
- Questions open session.

ICH Q9 and ICH Q10

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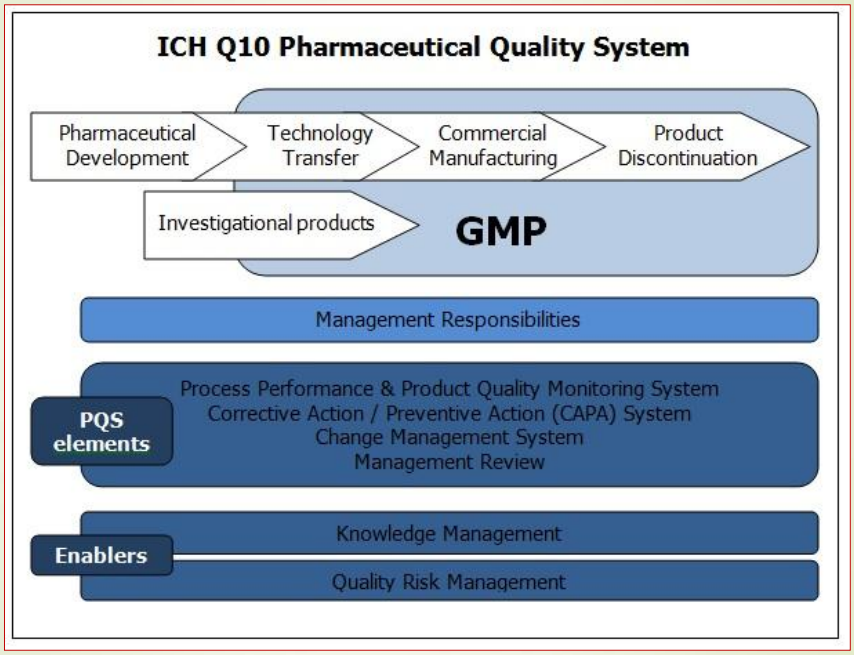
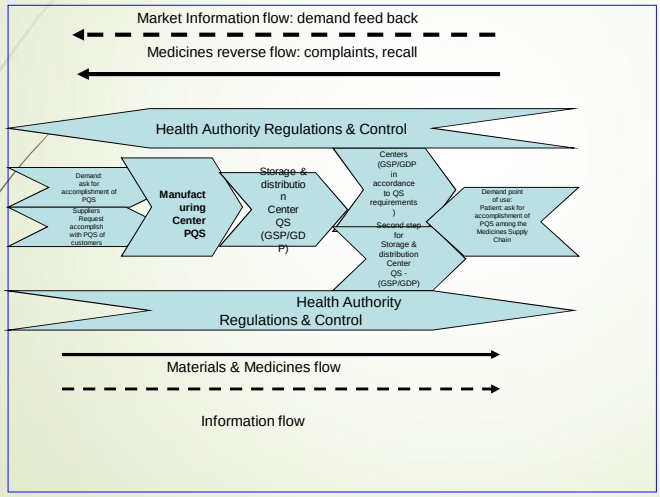


PQMS : Medicines supply chain management (MSCM) and Pharmaceutical Quality System



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

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

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Addressing Uncertainties and Challenges Related to Crucial Quality Check Points among the Quality System

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

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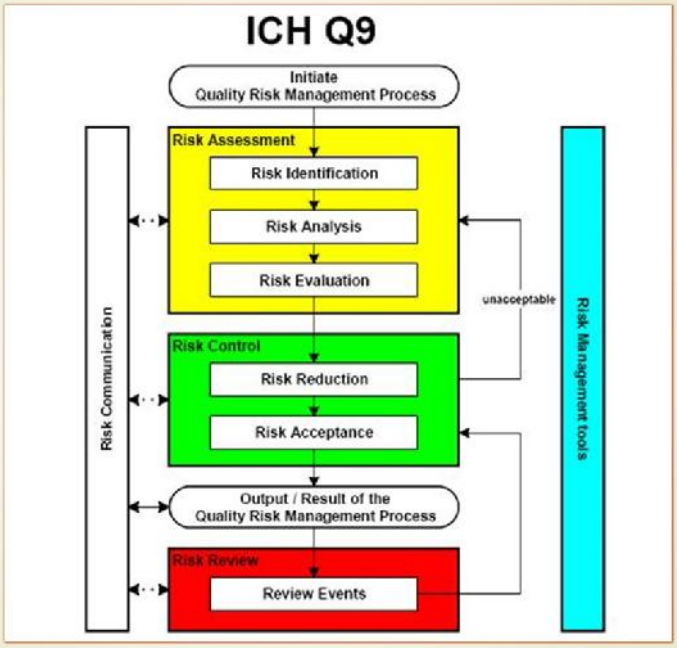

Management of risk process

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ICH Q9

Quality risk management supports a scientific and practical approach to decision making.

It provides documented, transparent, and reproducible methods to accomplish steps of the quality risk management process based on current knowledge about assessing the probability, severity, and, sometimes, detectability of the risk.

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Steps

- Define Scope
- Evaluate
- Reduce uncertainty
  - "risk under control"
  - "monitoring situations or critical elements that could lead to a risk"

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How can be defined the critical processes to work on?

- The ones that allows to run the business including social responsibility
- The ones that has indirect or direct impact in:
  - Public Health
    - Vaccines shortages
  - Environment
  - Private and Public economy

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Examples of Critical processes in the Pharmaceutical Quality System among the Supply chain management in vaccines

- Organization & responsibilities
- Premises layout including materials & personnel flow:
  - cleaning
- Process steps
- Documentation
- Qualifications & Validations
- Audits & CAPA Plan
- Sanitary vigilance

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Quality System Fundamentals and main documents

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Key steps in Pharmaceutical Quality System

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

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Conclusion:

Quality Management is a culture in the company supported in the Philosophy of Good Practices application

Tools in risk analysis

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Risk or Hazard?

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Risk

- ISO 14971:2000
  - Combination of the probability of occurrence of harm and the severity that this implies.
- Canadian Standards Association,2002
  - Possibility of damage or loss defined as a measure of the probability of occurrence and severity of adverse effects produced on the health, property, environment, organization, or other values.
    - image

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Risk characteristics

- Uncertainty
- Subjectivity
- What we mean by shareholders
- Controls on the risk

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Hazard

- Actual or potential condition that can cause injury, illness or death to persons, damage or loss in systems, equipment, or other public or private property, or environmental damage (Lamarca, 2000)

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Hazard II: characteristics

- It is an intrinsic part of a substance, situation, process
- There may be more of a hazard associated with them
- Evidential effects not immediately be observed
- It can generate a cascade effect
- It affects shareholders / Society in different ways

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"The investigation of risks is at once a scientific activity and an expression of culture" Kasperson, Renn, Slovic et al. (1988)

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Reduce uncertainty:

TOOLS FOR RISK ANALYSIS

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Classification

- Inductive
- Deductive
- Qualitative
- Quantitative

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- Origen in Medical Device and Engineering
  - Fault Tree Analysis (FTA)
  - Failure Mode and Effect Analysis (FMEA)
  - Failure Mode and Effect Criticality Analysis (FMECA)
- Origen in Food, Medicines & Pharmaceutical Process
  - RA (Risk analysis)
  - Hazard Analysis and Critical Control Point (HACCP)

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- Risk classes:
  patient
  operation
  financial
  regulatory
  others
- Risk undertanding as integral part of the process
- What does it mean "To have the risk under control"?

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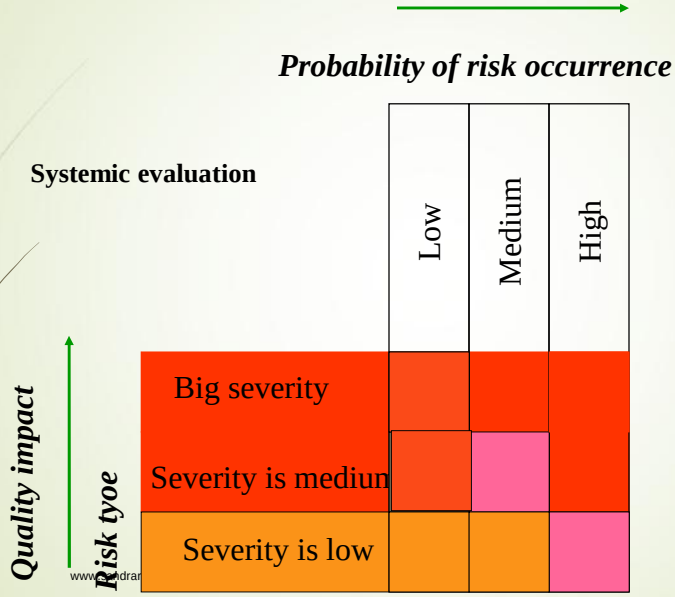

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Some concepts to take into account

- Equipment, Systems, Process
- Qualified personnel
- Process described: Flowchart
  - Specifications: Acceptance criteria
  - Process variability
- Change control system
- Validated status to be kept: APR

FTA (fault tree analysis)

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Fault Tree Analysis (FTA)

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- Deductive, top-down approach
- First it is assumed that there exists a failure
- Then identify the events that lead directly or indirectly to the failure
- The methodology can be applied to the investigation of deviations, complaints, findings for continuous improvement.

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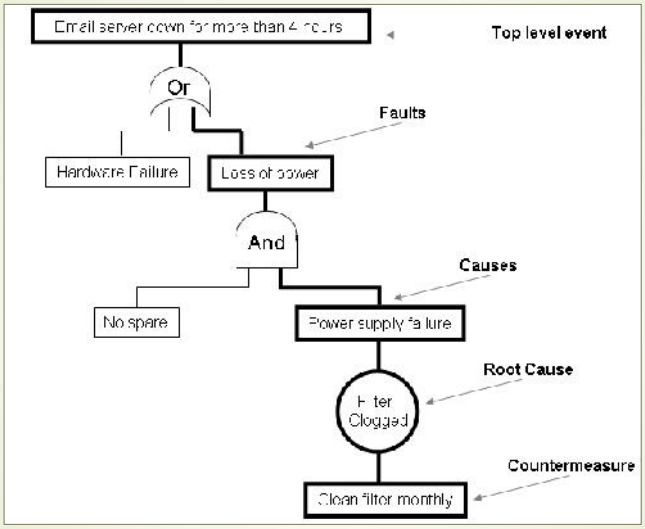

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- The garments at clean room entry were found with no identification of sterilization and last date to be used
- Differential pressure between grade B and C was found yesterday at 7Pa and today at 12 Pa. Yesterday an aspetic filling of a vaccine was done.
- The documentation from Site A it is not completed: vaccines storage data is not included and when you ask for having the docuemnt complete, they said they have no idea you`re speaking about.
- Large pools of frozen venoms, collected from many individuals, are allowed to thaw at 0 °C, to avoid proteolytic degradation of venom components and, after being thoroughly mixed, aliquots of liquid venoms are prepared. These aliquots are then freeze-dried and stored in the dark at a low temperature (either -20 °C or 4 °C). Aliquots of freeze-dried venoms should be adequately labelled as per specification. The storage conditions of the venoms you used ask for (2-8)ºC. Once serum manufacturing process is running you detected in the documentation preparation and review that the temperature of venoms was not reported, you asked it to the WH and the temperature control shows you data of 3 days at 7ºC and then 3 days at 9ºC.

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Pre RA(Pre- risk analysis)

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Pre RA:
Based on what if questions

- Requires knowledge of the process
- Apply from brainstorming process
- Flowchart
- Interdisciplinary Team
- Qualitative
- Identifies event possibilities and describes the probability of occurrence

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Pre- RA : steps

- Process description
- Risk scenarios List
- Risk prevention meassures identification
- To evaluate the results and establish that risks will be “remove" and / or control in a given process
- Document the analysis process

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Typical design form

Columns were extracted study only.

Header orresponds to the system under analysis, date, in charge staff, and at the foot firms/date must be included.

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I

Step	Potential risk	Justification of the risk, how to manage the risk	Ponderation (L;M;H) (1, 2,3)	Follow up yes or not

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II

Step	Test to be done	Responsible/ dtae	AC	Result found

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Failure Mode and Effect Analysis (FMEA)

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Failure Mode and Effect Analysis (FMEA)

- Systematic and analytical methodology that can prevent failures
- Preventive non reactive

Form example

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Failure Mode and Effect Analysis (FMEA)

SYSTEM DESCRIPTION: Bior PW **DATE:** 20 . June,2012

REFERENCES: USP XXIX

COMPILED BY: MS **REVIEWED BY:** MEA

step	conditions	potential fault	level afected	potential causes of risk	controls that are in force	history	severity and jsutification (H;M;L)	possibility of detection of the failure	priority in risk analysis (enumerate)
sampling	qualified staff	microbial contamination	stop operation	OOS	training	OOS/APR	H	H late	1
								L early	

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FMECA
–failure mode effects and critically analysis-

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To be used when?

- Design building / support systems
- New processes
- To Evaluate performance of services
- After Other tools

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How to use it…

- Define the universe of study
- Identify potential fault models and its effects Set the RPN
- Risk management monitoring
- Control and monitoring
- Document

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Building probability, severity and detectability tables in vaccines manufacturing

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Risk analysis vs. Risk assessment

Risk assessment is a step in a risk management procedure. Risk assessment is the determination of quantitative or qualitative value of risk related to a concrete situation and a recognized threat (also called hazard).

Quantitative risk assessment requires calculations of two components of risk *(R):*, the magnitude of the potential loss *(L) named as severity (S)* and the probability *(p)* that the loss will occur. In addition the availability of detect it must be considered (D).

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Form example

FMECA

SYSTEM DESCRIPTION: Bior PW **DATE:** 20 . June,2012

REFERENCES: USP XXIX

COMPILED BY: MS **REVIEWED BY:** MEA

step	conditions	potential fault	level afected	potential causes of risk	controls that are in force	Probability	severity	possibility of detection of the failure	RPN
sampling	qualified staff	microbial contamination	stop operation	OOS	training	2	3	3 late	18
						2	3	1 early	6

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- WFI loop modification: from a change control for a new point of use related a CIP SIP (new installation)
- CT Protocol modification was approved by HA, as a result additional samples of blood should be collected every 3 days instead of once/week. Your sites should be instructed and documentation follow up is required.

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HACCP
-hazard analysis and critical control points-

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7 principles of HACCP

1. Perform risk analysis on the process flow
2. Determine critical points (critical control points (CCPs)
3. Set limits for these critical points
4. Establish monitoring systems thereof
5. Establish corrective actions
6. Establish verification procedures
7. Set the document support

HACCP main forms after flowchart is done

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Establishing the risk priority number

Hazards	RPN determination P	S	?	RPN	Cause / Justification	Preventive measure

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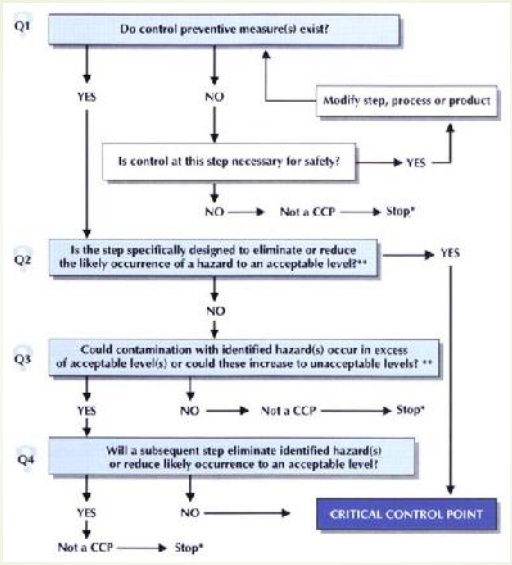

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Step	HAZARD	Decision tree				PCC	N°	Observations
		Q1	Q2	Q3	Q4			

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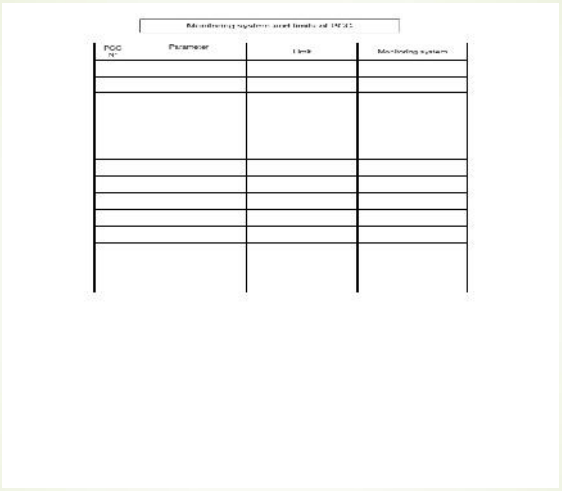

PCC nr	Parameter	Limit	Monitoring system

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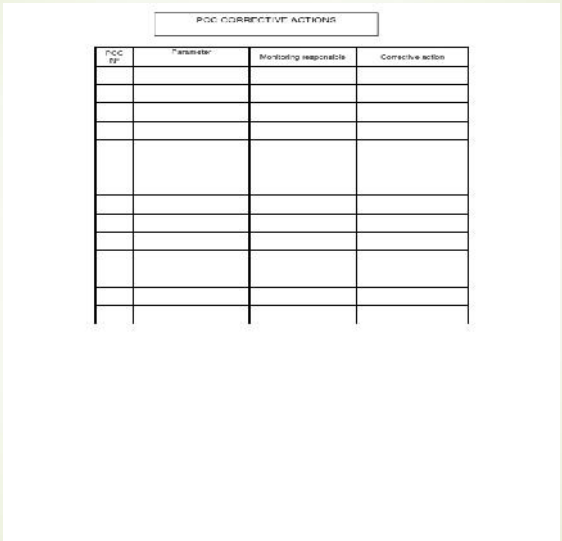

PCC CORRECTIVE ACTIONS

PCC nr	Parameter	Monitoring responsible	Corrective action

Exercise: HACCP

Aseptic filling of OPV
FD process for BCG
Bulk mixer cleaning process with CIP SIP in vaccines
Media fill interventions planning
CT protocol release and communication to sites

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Final discussion

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Why and where we fault?

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Exercise: HACCP

Media fill risk assessment

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Questions: open session.

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Thank you!

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