MODULE 1

QUALIFICATION AND VALIDATION CONCEPTS

The objectives of this workshop

1. Elevate our industry to more knowledge,
2. better understanding of our manufacturing systems
3. Focus on what's important (Critical)
4. *More is not better*
5. Better technical understanding (Subject Matter Experts)

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QUESTION :
HOW CAN THE GROUPS HELP YOU IN REACHING THESE OBJECTIVES ?

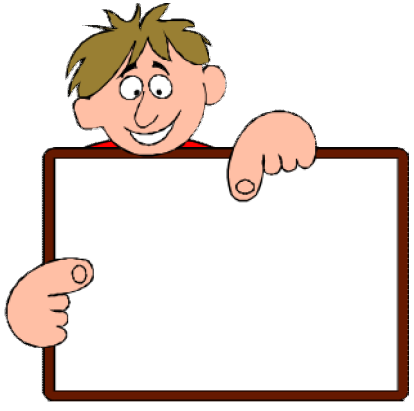
This workshop is not a how to do guide

1. You should develop your appropriate systems and procedures and not get “ready to use” procedures.

2. You should develop tools and templates.

GOOD NEWS : A LOT OF ANSWERS

ARE ALREADY IN …..



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1. You should develop your appropriate systems and procedures and not get ready to use procedures.

2. You should develop tools and templates.

GOOD NEWS : A LOT OF ANSWERS

ARE ALREADY IN ……

The beauty of ICH Q10

1. Where to go
2. How to go
3. Enablers.
4. Risk assessment

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) is unique in bringing together the [redacted] to discuss scientific and technical aspects of drug registration. Since its inception in 1990, ICH has gradually evolved, to respond to the increasingly global face of drug development, so that the benefits of international harmonisation for better global health can be realised worldwide. ICH's mission is to achieve greater harmonisation to ensure that safe, effective, and high quality medicines are developed and registered in the most resource-efficient manner

ICH
harmonisation for better health

About ICH | Work Products | Meetings | Training | Newsroom

ICH Guidelines / Work Products /

The ICH topics are divided into four categories and ICH topic codes are assigned according to these categories.

Quality Guidelines

Harmonisation achievements in the Quality area include pivotal milestones such as the conduct of stability studies, defining relevant thresholds for impurities testing and a more flexible approach to pharmaceutical quality based on Good Manufacturing Practice (GMP) risk management.

Safety Guidelines

ICH has produced a comprehensive set of safety Guidelines to uncover potential risks like carcinogenicity, genotoxicity and reprotoxicity. A recent breakthrough has been a non-clinical testing strategy for assessing the QT interval prolongation liability: the single most important cause of drug withdrawals in recent years.

Efficacy Guidelines

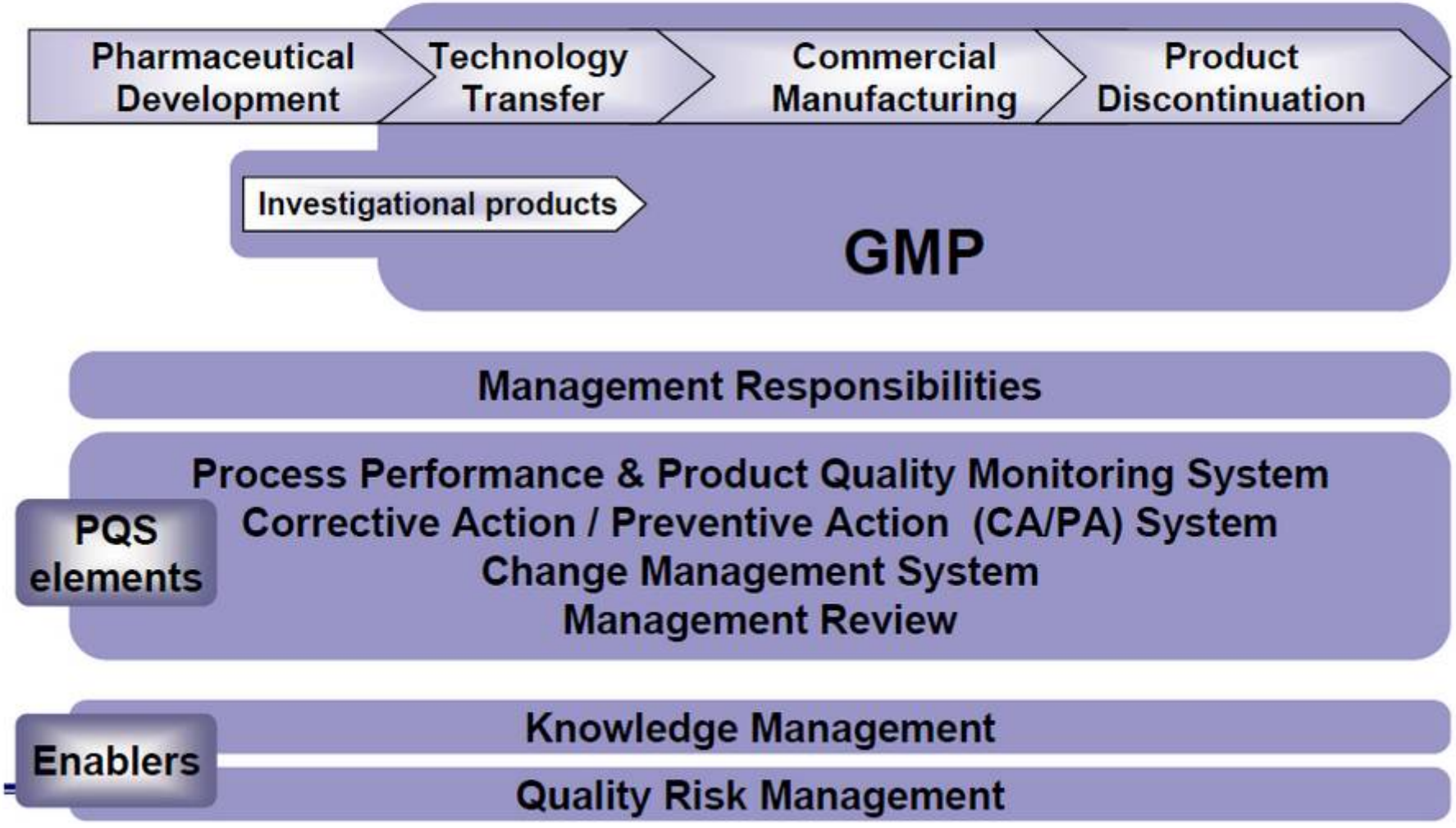
The work carried out by ICH under the Efficacy heading is concerned with the design, conduct, safety and reporting of clinical trials. It also covers novel types of medicines derived from biotechnological processes and the use of pharmacogenetics/genomics techniques to produce better targeted medicines.

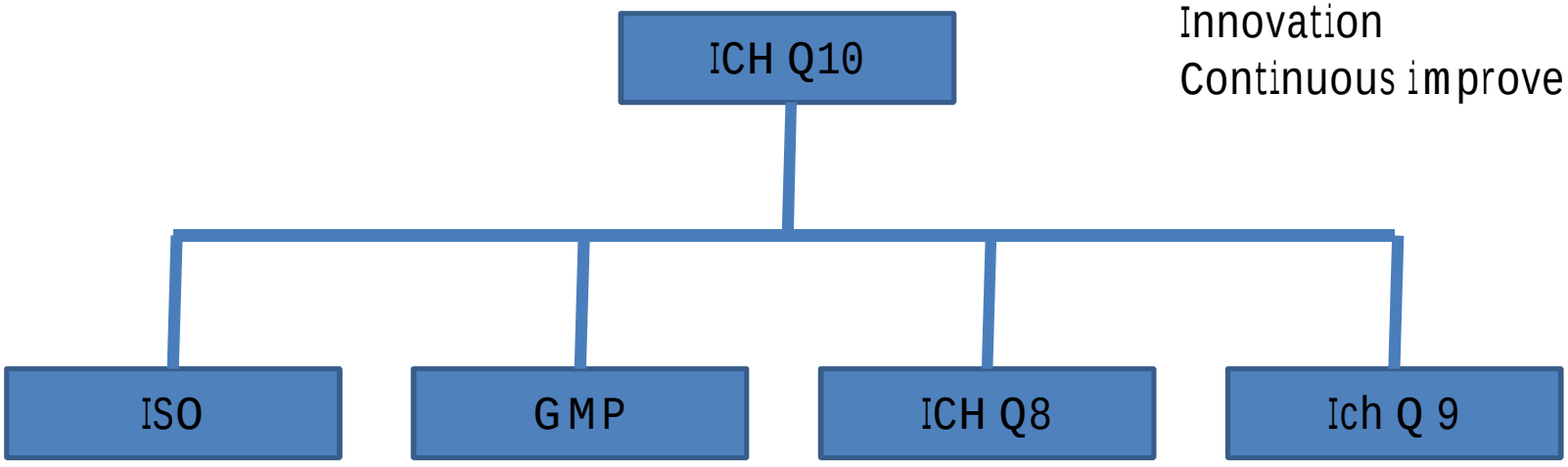
Multidisciplinary Guidelines

Those are the cross-cutting topics which do not fit uniquely into one of the Quality, Safety and Efficacy categories. It includes the ICH medical terminology (MedDRA), the Common Technical Document (CTD) and the development of Electronic Standards for the Transfer of Regulatory Information (ESTRI).

- Q1A - Q1F Stability
- Q2 Analytical Validation
- Q3A - Q3D Impurities
- Q4 - Q4B Pharmacopoeias
- Q5A - Q5E Quality of Biotechnological Products
- Q6A- Q6B Specifications
- Q7 Good Manufacturing Practice
- Q8 Pharmaceutical Development
- Q9 Quality Risk Management
- [redacted]
- Q11 Development and Manufacture of Drug Substances
- Q12 Lifecycle Management
- Cross-cutting Topics

ICH Q10 PQS


Pharmaceutical Development
Technology Transfer
Commercial Manufacturing
Product Discontinuation
Investigational products
GMP
Management Responsibilities
PQS elements
Process Performance & Product Quality Monitoring System
Corrective Action / Preventive Action (CA/PA) System
Change Management System
Management Review
Enablers
Knowledge Management
Quality Risk Management



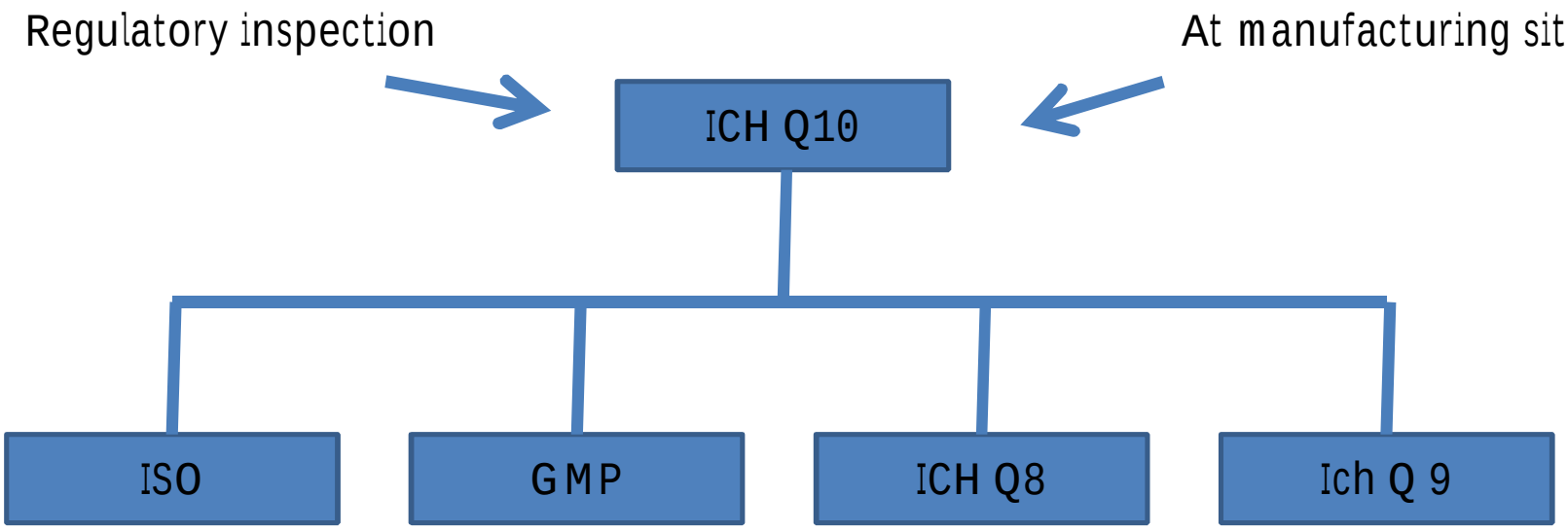
Innovation
Continuous improvement

Pharmaceutical development

Quality risk management

Management responsibilities.

Lifecycle

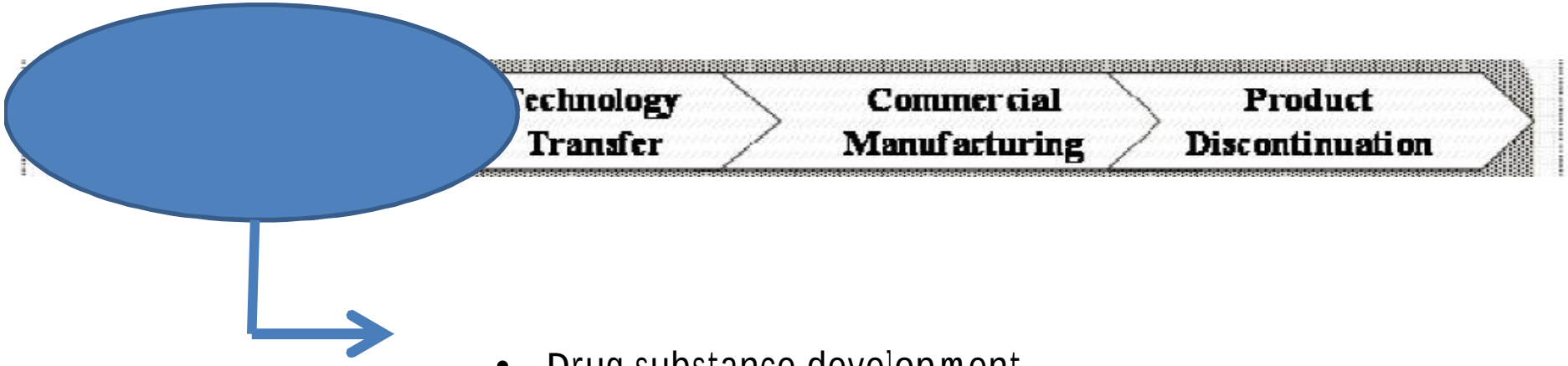

Regulatory inspection
At manufacturing site
ICH Q10
ISO
GMP
ICH Q8
Ich Q 9

Integration of Q8, Q9, & Q10

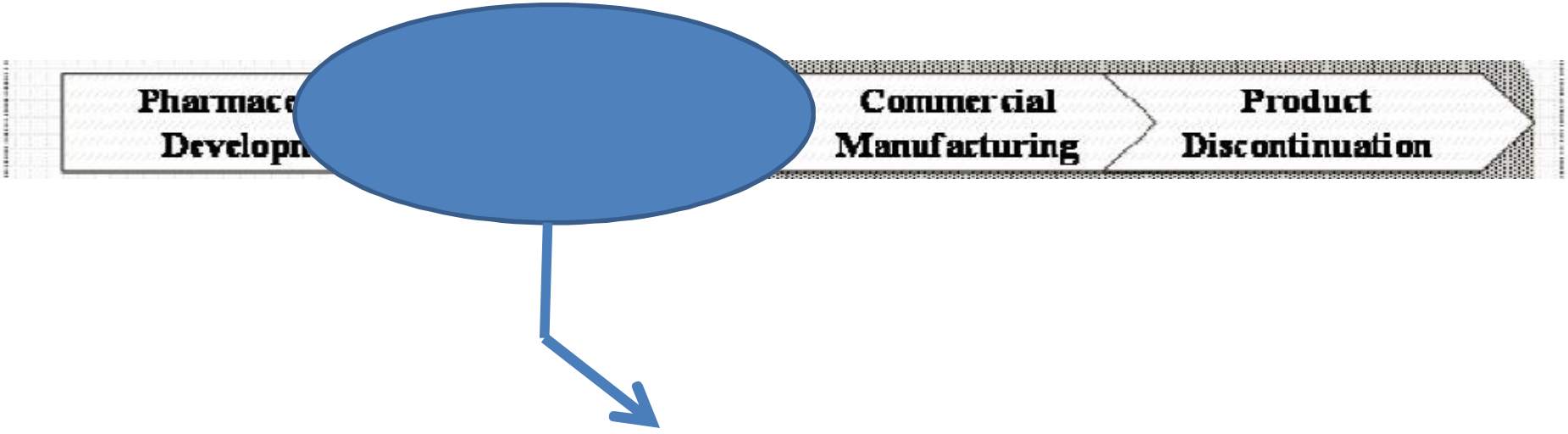
- An integrated set of guidelines:
  - Q8 Pharmaceutical Development
  - Q10 Pharmaceutical Quality Systems
- Q8, 9, & 10:
  - Risk Management, and PQS provide greater product assurance of quality

Integration of Q8, Q9, & Q10 (continued)

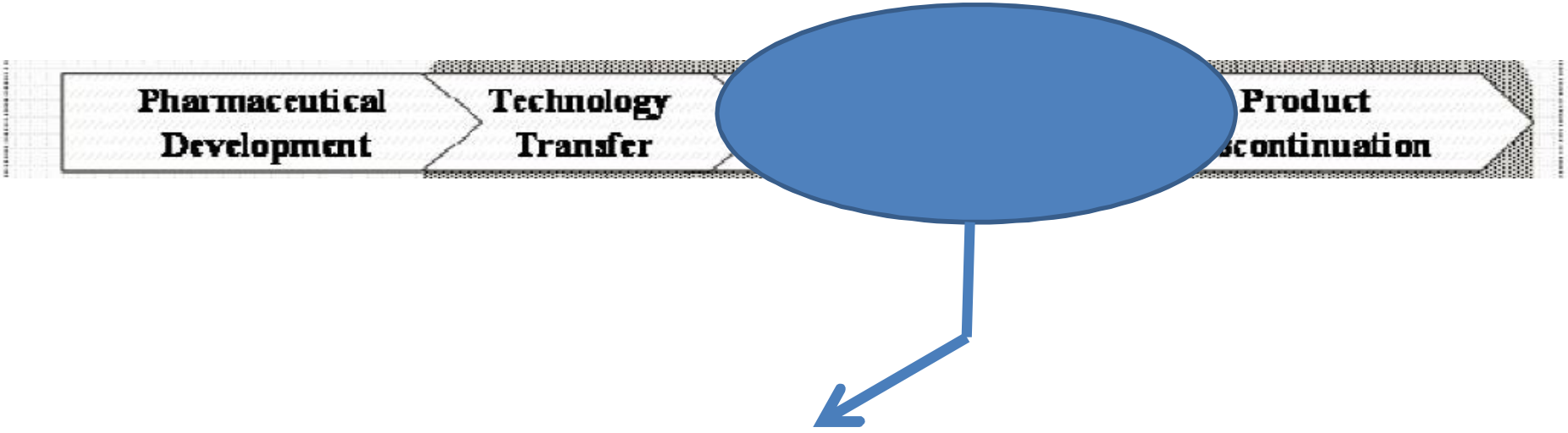
- Q8 & 10:
  - Processes for pharmaceutical development are key linkages to product realization within the PQS.
  - Q8 provides for robust development and understanding th[illegible] as the basis for [illegible].
  - Manufacturers with a robust PQS and appropriate process knowledge can implement many types of [illegible]
- Q9 & 10:
  - The PQS should encourage and facilitate the use of [illegible] appro[illegible]out the system.
  - The design and application of processes within the PQS should be based on [illegible]



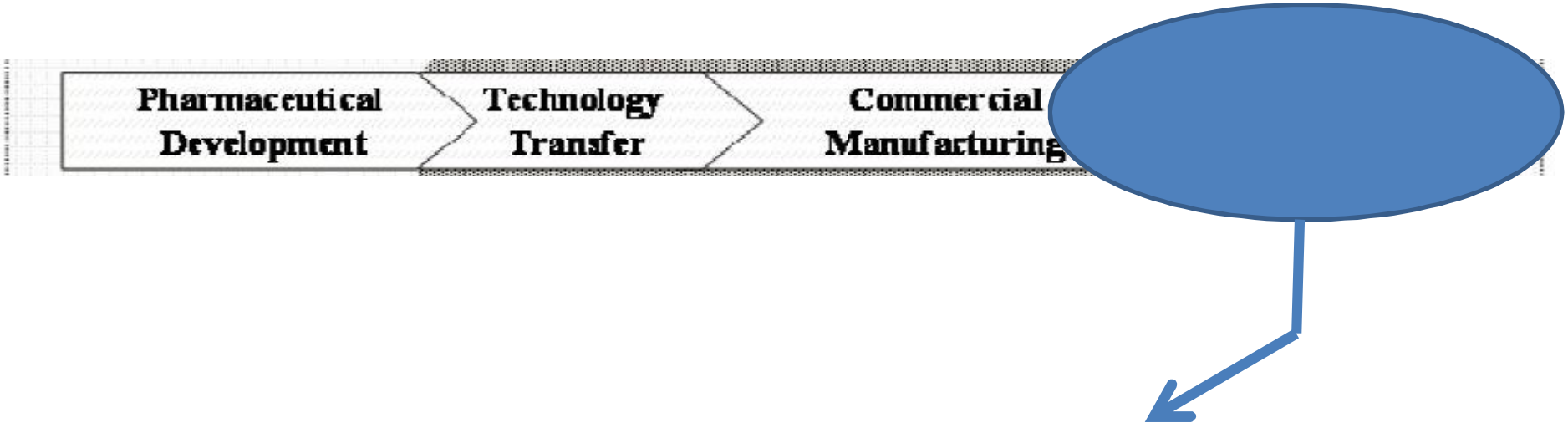
- Drug substance development.
- Formulation development.
- Manufacture of investigational products.
- Delivery system development.
- Manufacturing process development and scale up
- Analythical method development.



- New product transfers during development through manufacturing.
- Transfers within or betwinn manufacturing and testing sites for marketed products.

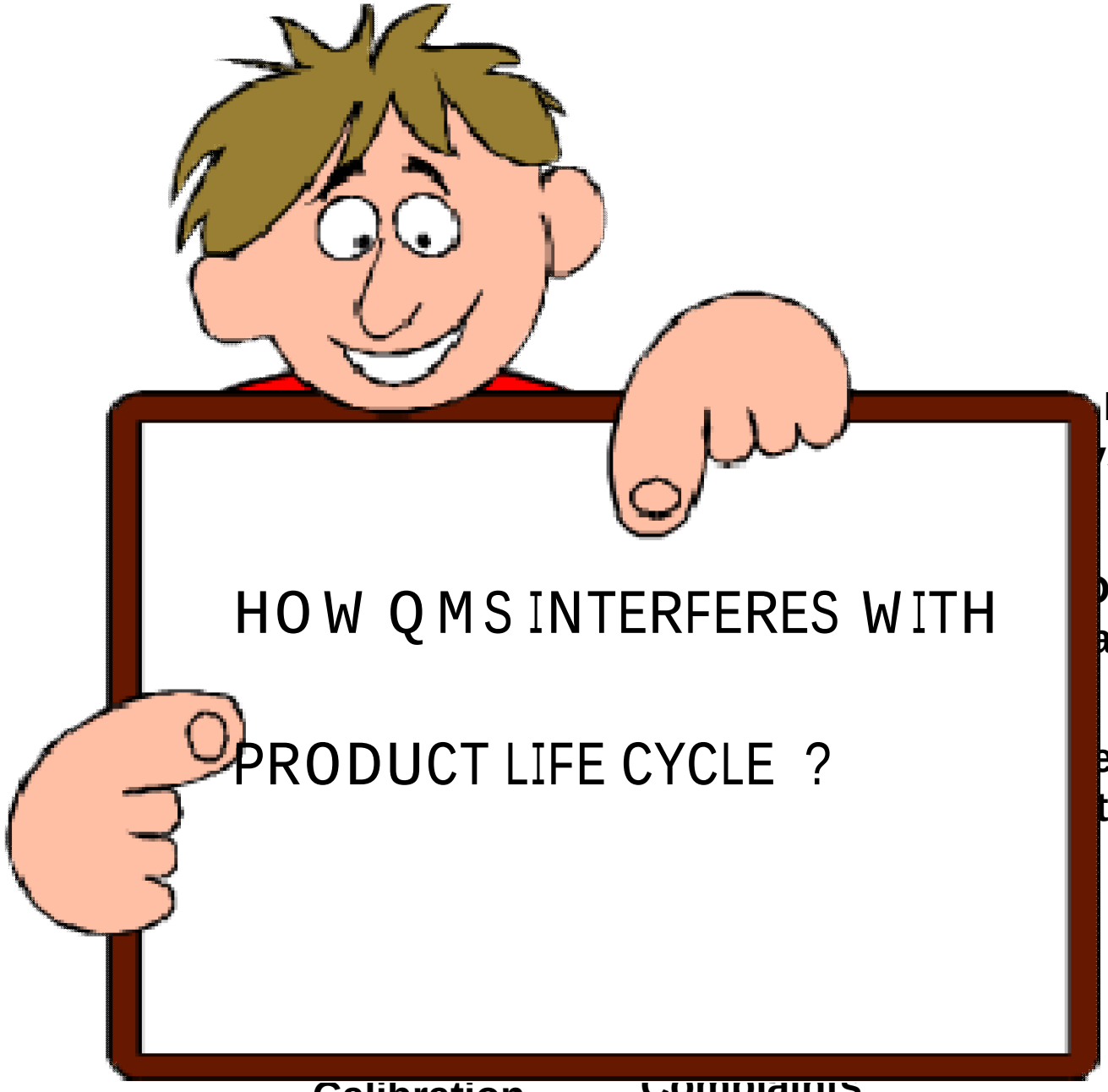


- Acquisition and control of materials
- Provision of facilities, utilities and equipment
- Production
- Quality control and assurance.
- Release
- Storage
- Distribution.



- Retention of documentation
- Sample retention
- Continued product assessment and reporting

ICH Q10 OBJECTIVES



M

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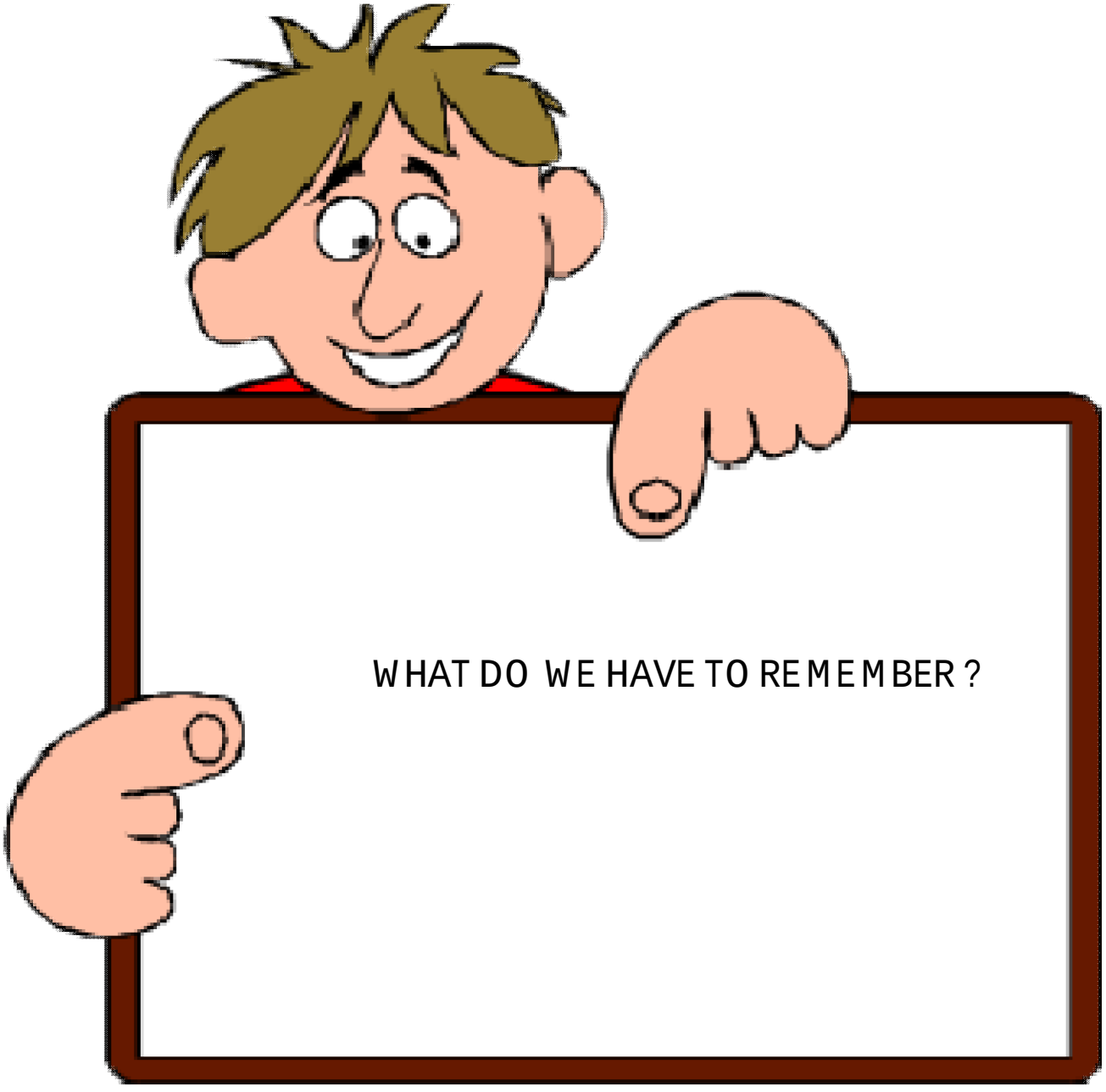
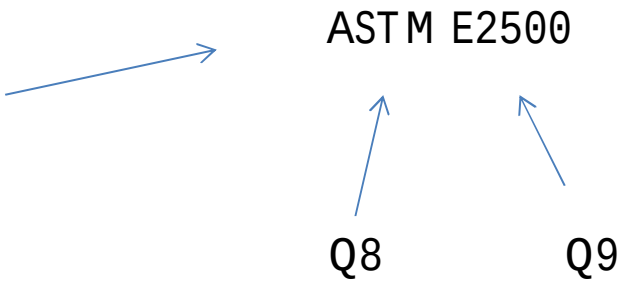
Calibration

Complaints

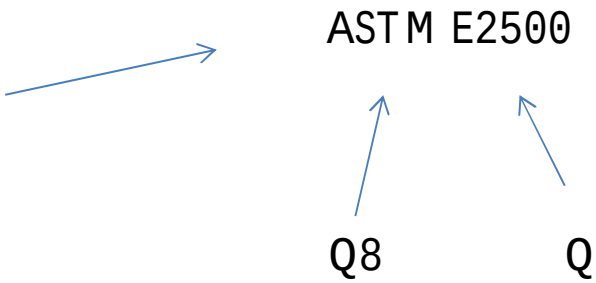

WHAT DO WE HAVE TO REMEMBER?

REMEMBER THE KEY CONCEPTS :



1. RISK BASED APPROACH.
2. SCIENCE BASED APPROACH.
3. CRITICAL ASPECTS OF MANUFACTURING SYSTEMS
4. QUALITY BY DESIGN
5. GOOD ENGINEERING PRACTICES
6. SUBJECT MATTER EXPERT
7. USE OF VENDOR DOCUMENTATION
8. CONTINUOUS PROCESS IMPROVEMENT

REMEMBER THE KEY CONCEPTS :



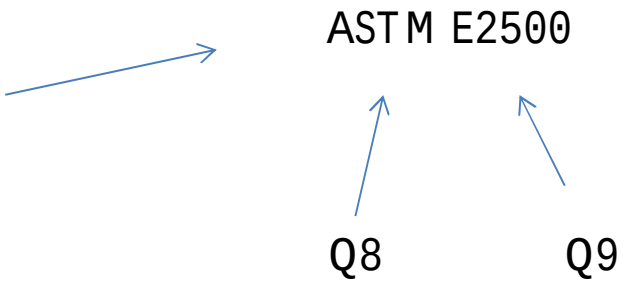
1 RISK BASED APPROACH.

APPLIED APPROPRIATELY AT EACH STAGE

BASED ON SCIENTIFIC KNOWLEDGE

PROTECTION OF THE PATIENT

REMEMBER THE KEY CONCEPTS :



2 SCIENCE BASED APPROACH.

CONSIDER	CRITICAL QUALITY ATTRIBUTES	CQA
	CRITICAL PROCESS PARAMETERS	CPK

2 SCIENCE BASED APPROACH.

CRITICAL QUALITY ATTRIBUTES CQA

Process and equipment capability : CPK

2 SCIENCE BASED APPROACH.

Use of statistics

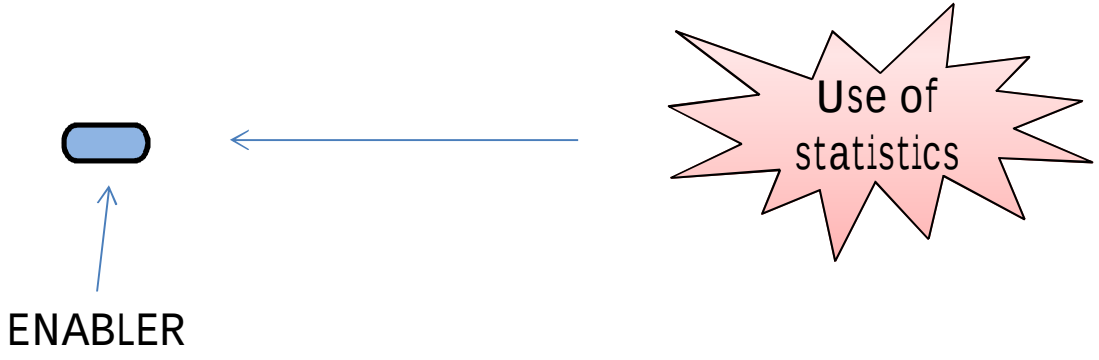
CRITICAL QUALITY ATTRIBUTES CQA

Process and equipment capability : CPK

In process improvement efforts, the process capability index or process capability ratio is a statistical measure of process capability: the ability of a process to produce output within specification limits.

Wikipedia

2 SCIENCE BASED APPROACH.



Wikipedia

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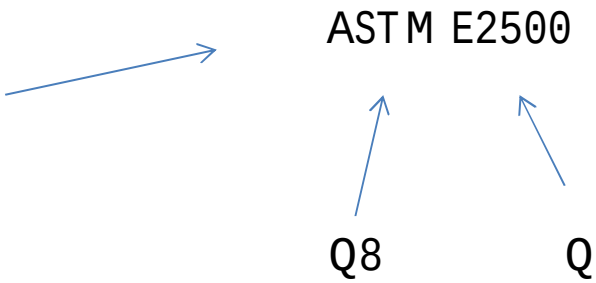
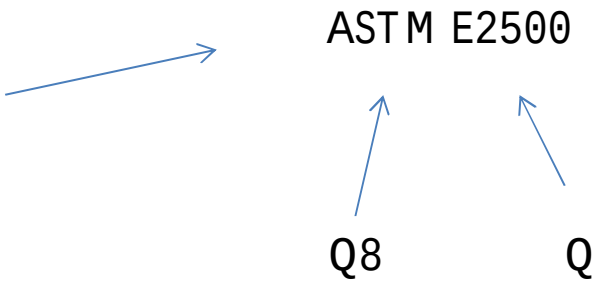


2 SCIENCE BASED APPROACH.

CONSIDER CRITICAL PROCESS PARAMETERS CPP

REMEMBER THE KEY CONCEPTS :



2 SCIENCE BASED APPROACH.

CONSIDER CRITICAL PROCESS PARAMETERS CPP

STATISTICAL TRENDING

IN « BEST IN CLASS » IT IS NOT SUFFICIENT TO DEMONSTRATE THAT THE SYSTEM IS UNDER CONTROL « WITHIN ITS CRITICAL PARAMETERS INFLUENCING THE CRITICAL QUALITY ATTRIBUTES » BUT IT IS GOOD PRACTICE TO MONITOR THE STATISTICAL TRENDING.

IS MY PROCESS DRIFTING ?

REMEMBER THE KEY CONCEPTS :

ASTM E2500

Q8 Q9

2 SCIENCE BASED APPROACH.

AGAIN : SCIENCE AND STATISTICS ARE ENABLERS TO HELP YOU CONTROLLING AND PREDICTING YOUR PROCESS

ENABLER

ASTM E2500

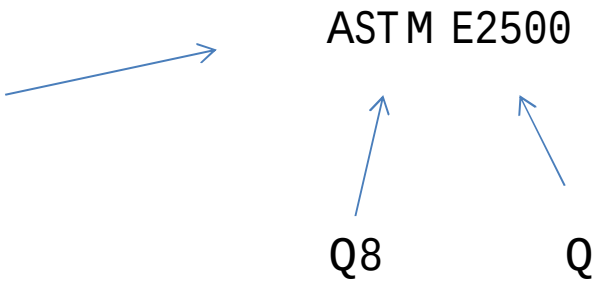
REMEMBER THE KEY CONCEPTS :

Q8 Q9

3 CRITICAL ASPECTS OF MANUFACTURING SYSTEMS

VERIFICATION ACTIVITIES SHOULD FOCUS ON THESE ASPECTS AND SHOULD BE DOCUMENTED

REMEMBER THE KEY CONCEPTS :



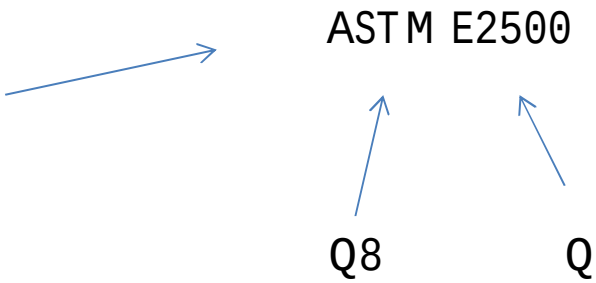
4 QUALITY BY DESIGN

CRITICAL ASPECTS ARE DESIGNED INTO SYSTEMS DURING THE

SPECIFICATIONS AND DESIGN PROCESS.... ASSOCIATED WITH ACCEPTANCE CRITERIA

ASSURANCE THAT MANUFACTURING SYSTEMS ARE FIT FOR INTENDED USE SHOULD NOT RELY SOLELY UPON VERIFICATION AFTER INSTALLATION BUT BE ACHIEVED BY A PLANNED AND STRUCTURED VERIFICATION APPROACH APPLIED THROUGHOUT THE SYSTEM LIFE CYCLE;

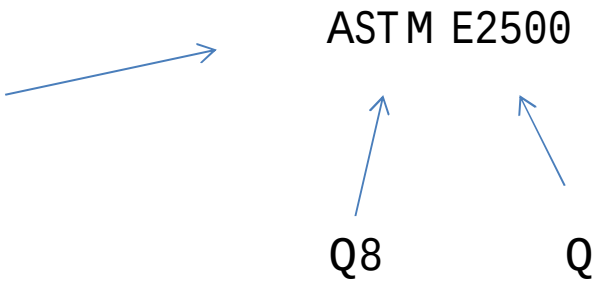
REMEMBER THE KEY CONCEPTS :



5 GOOD ENGINEERING PRACTICES

ESTABLISHED ENGINEERING METHODS AND STANDARDS THAT ARE APPLIED THROUGHOUT THE LIFE CYCLE TO DELIVER APPROPRIATE AND EFFECTIVE SOLUTIONS

REMEMBER THE KEY CONCEPTS :

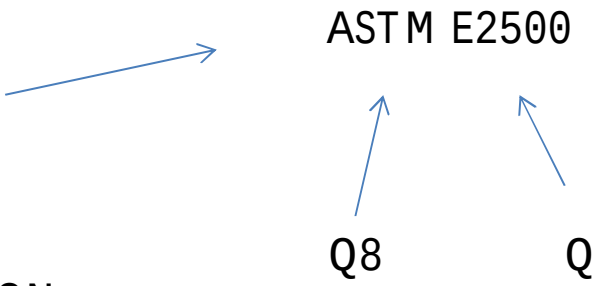


6 SUBJECT MATTER EXPERT

INDIVIDUALS WITH SPECIFIC EXPERTISE AND RESPONSIBILITY IN A PARTICULAR AREA OR FIELD :

- ENGINEERING
- QUALITY
- AUTOMATION
- OPERATIONS
- ...

REMEMBER THE KEY CONCEPTS :



7 USE OF VENDOR DOCUMENTATION

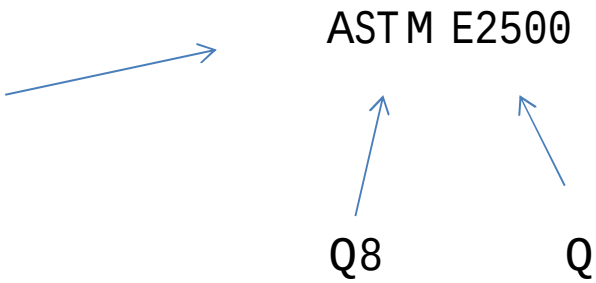
VENDOR DOCUMENTATION INCLUDING TEST DOCUMENTS MAY BE USED AS PART OF THE VERIFICATION DOCUMENTATION PROVIDING THE REGULATED COMPANY HAS ASSESSED THE VENDOR AND HAS EVIDENCE OF :

ACCEPTABLE VENDOR QUALITY SYSTEM

VENDOR TECHNICAL CAPABILITY

VENDOR APPLICATION OF GEP

REMEMBER THE KEY CONCEPTS :

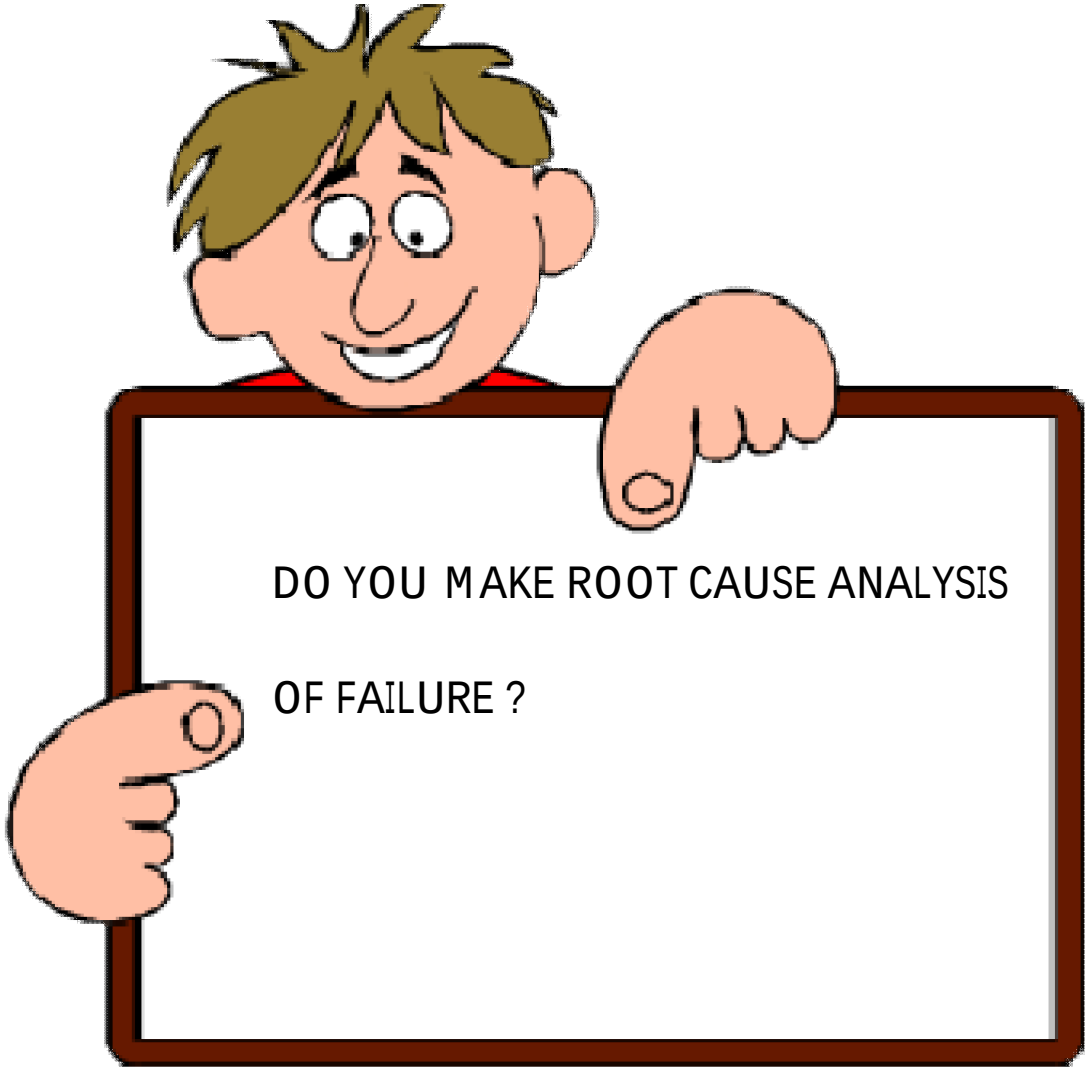


8 CONTINUOUS PROCESS IMPROVEMENT

OPORTUNITY FOR IMPROVEMENT SHOULD BE SOUGHT BASED ON PERIODIC REVIEW AND EVALUATION, OPERATIONAL AND PERFORMANCE DATA, AND ROOT-CAUSE ANALYSIS OF FAILURE.

CHANGE MANAGEMENT SHOULD PROVIDE A DEPENDABLE MECHANISM FOR PROMPT IMPLEMENTATION....

ROOT-CAUSE ANALYSIS OF FAILURE



TRICK – FOR ROUTE CAUSE ANALYSIS OF FAILURE

THE 6 WHY

EX : WE FAILED A MEDIA FILL

WHY 1 : BECAUSE WE HAD A POLLUTION ON A FILLING NEEDLE

WHY 2 : BECAUSE WE HAD A BAD STEAM STERILIZATION

WHY 3 : BECAUSE THE STEAM FLOW WAS NOT BALANCED PROPERLY

WHY 4 : BECAUSE WE CHANGED A NEEDLE BEFORE THE STERILIZATION

WHY 5 : BECAUSE THE NEW NEEDLE WAS SLIGHTHY DIFFERENT

WHY 6 : BECAUSE THE NEEDLE DRAWING WAS NOT CORRECT

Objective one

ACHIEVE PRODUCT REALISATION

To establish, implement and maintain a system that allows the delivery of products With the [redacted] appropriate to meet the needs of patients, health care professionals, regulatory authorities and other internal or external customers.

Objective two

ESTABLISH AND MAINTAIN A STATE OF CONTROL

To develop and use effective monitoring and control systems for process performance and product quality, thereby providing assurance of continued suitability and capability of processes.

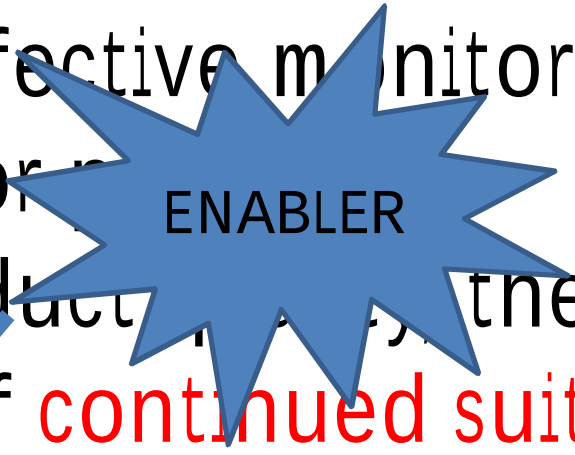
[redacted] can be useful in identifying the monitoring and control systems.

Objective two

ESTABLISH AND MAINTAIN A STATE OF CONTROL

To develop and use effective monitoring and control systems for [illegible] performance and product [illegible] thereby providing assurance of continued suitability and capability of processes.

can be useful in identifying the monitoring and control systems.



ENABLER :

A tool or process which provides the means to achieve an objective

ENABLER :

A [redacted] or process which provides the means to achieve an objective

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ENABLER :

A tool or [redacted] which provides the means to achieve an objective

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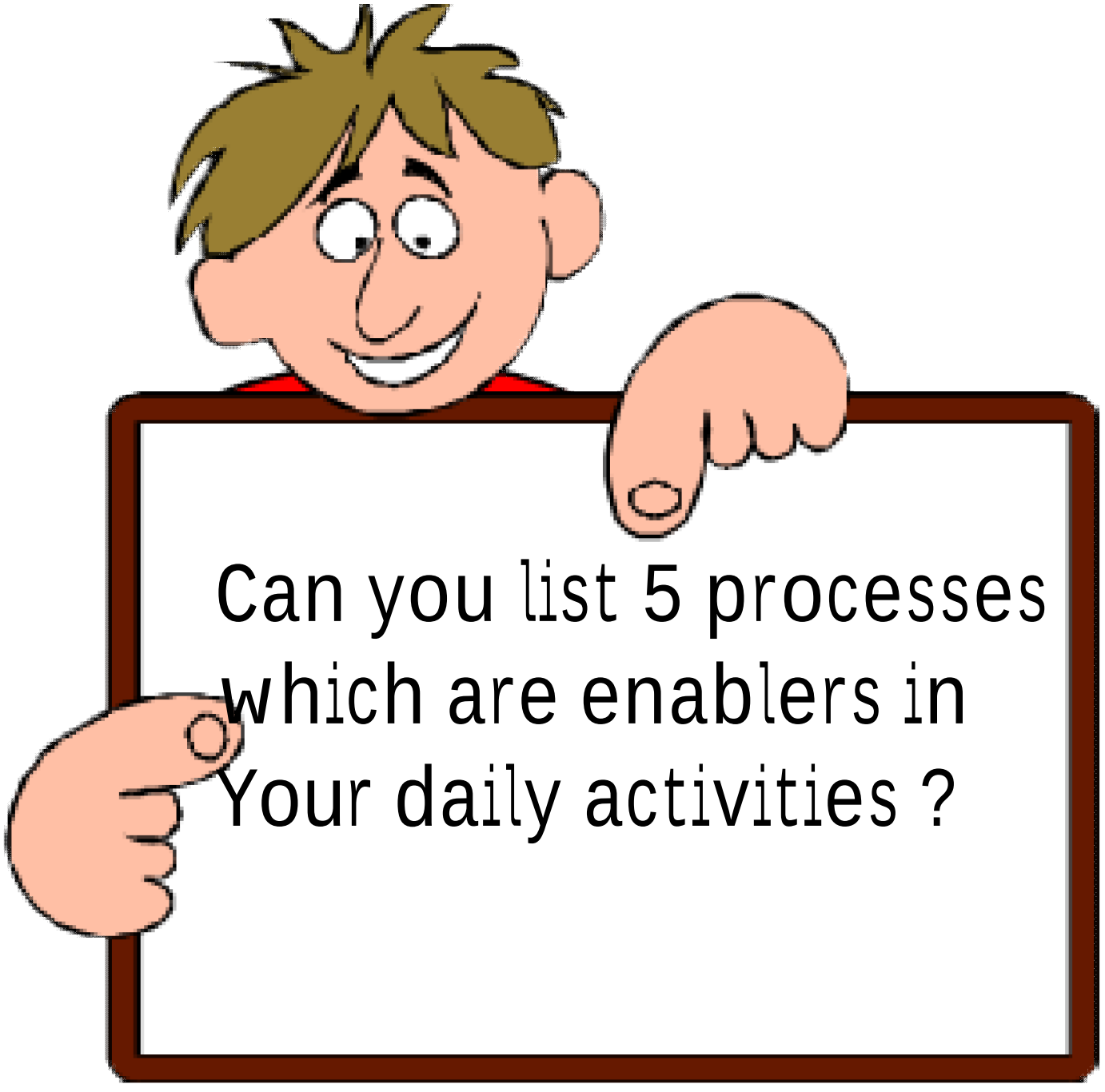

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Objective three

FACILITATE CONTINUAL IMPROVEMENT

To identify and implement [redacted] improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancement, thereby increasing the ability to fulfil quality needs consistently.

Objective three

FACILITATE CONTINUAL IMPROVEMENT

To identify and implement product quality improvements, [redacted] variability reduction, innovations and pharmaceutical quality system enhancement, thereby increasing the ability to fulfil quality needs consistently.

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FACILITATE CONTINUAL IMPROVEMENT

To identify and implement product quality improvements, process improvements, [redacted] innovations and pharmaceutical quality system enhancement, thereby increasing the ability to fulfil quality needs consistently.

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To identify and implement product quality improvements, process improvements, variability reduction, [redacted] and pharmaceutical quality system enhancement, thereby increasing the ability to fulfil quality needs consistently.

Objective three

FACILITATE CONTINUAL IMPROVEMENT

To identify and implement product quality improvements, process improvements, variability reduction, innovations and [redacted] enhancement, thereby increasing the ability to fulfil quality needs consistently.

Objective three

FACILITATE CONTINUAL IMPROVEMENT

To identify ..... consistently.

Quality risk management can be useful for identifying and prioritising areas for continual improvement.

Ol

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To iden

Quality
identify
continu

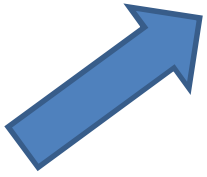
Knowledge management

- Acquiring.
- Analysing.
- Storing.
- Dissiminating

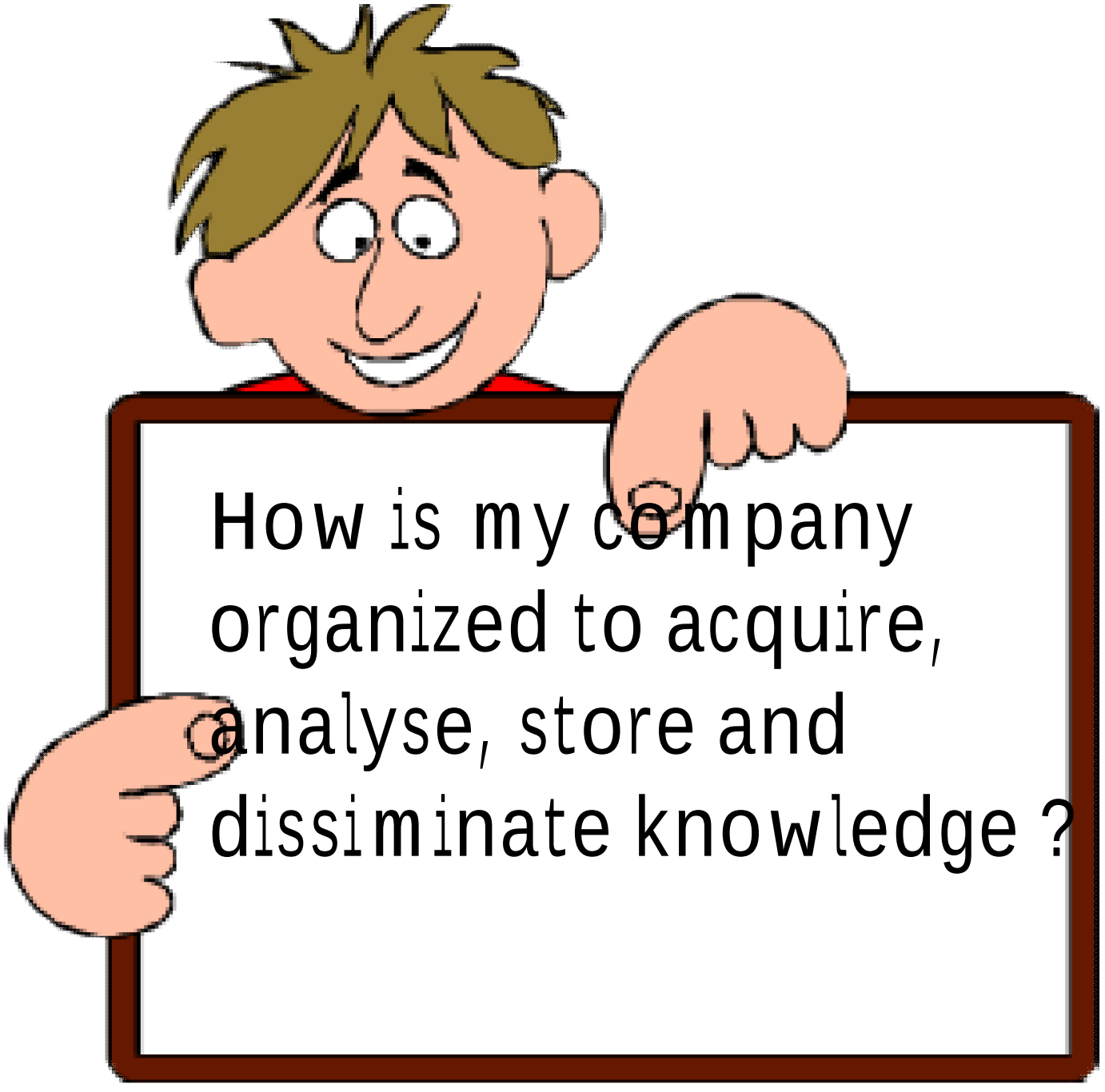
INFORMATION RELATED TO PRODUCTS

Knowledge management

INFORMATION RELATED TO PRODUCTS



- Public domain.
- Pharmaceutical development studies.
- Technology transfer activities.
- Process validation studies.
- Manufacturing experience.
- Innovation.
- Continual improvement
- Change management


How is my company organized to acquire, analyse, store and dissiminate knowledge ?

Knowledge management

- Public domain. → Regulatory affairs.
- Pharmaceutical development studies. → R&D
- Technology transfer activities. → Technical support dpt
- Process validation studies. → Technical support dpt
- Manufacturing experience. → Manufacturing dpt
- Innovation. → R&D
- Continual improvement → Quality dpt
- Change management → Quality dpt

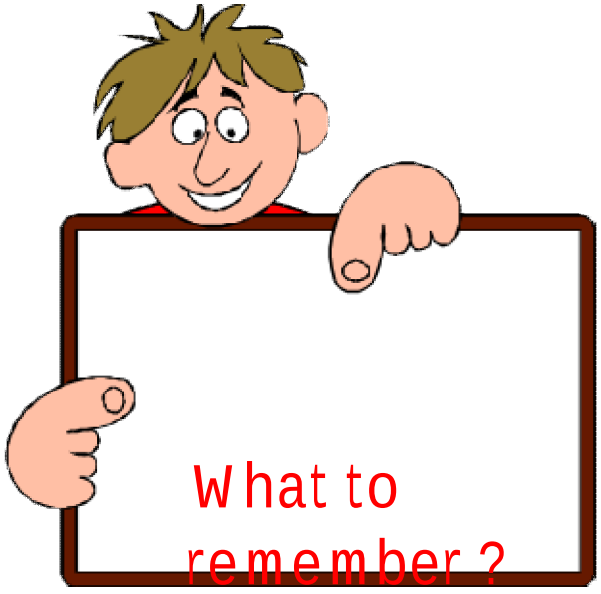
Quality risk management

Provide a proactive approach to identifying, scientifically evaluating and controlling potential risks to quality.

ICH Q9

Risk Management must be integrated into the Quality Management Systems

Quality risk management
What to remember



1. Minimum essentials
2. Manageable approach
3. One Size. . .
4. Risk & requirements
5. Risk-Based procedures
6. Incremental risk assessments
7. Into current processes
8. Of little value if . . .

Take away

- Identify problems
- Evaluate causes
- Estimate consequences
- Define & implement safeguards

Q

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1. Minim

2. Mana ents

3. One S

4. Risk &

It is not a one person activity.

The team must have a good knowledge :
Involve the subject matter experts.

If it is not followed by MITIGATION strategy supported by management it is a waste of energy.

It must be implemented, verified and followed by a responsible person reporting to management.

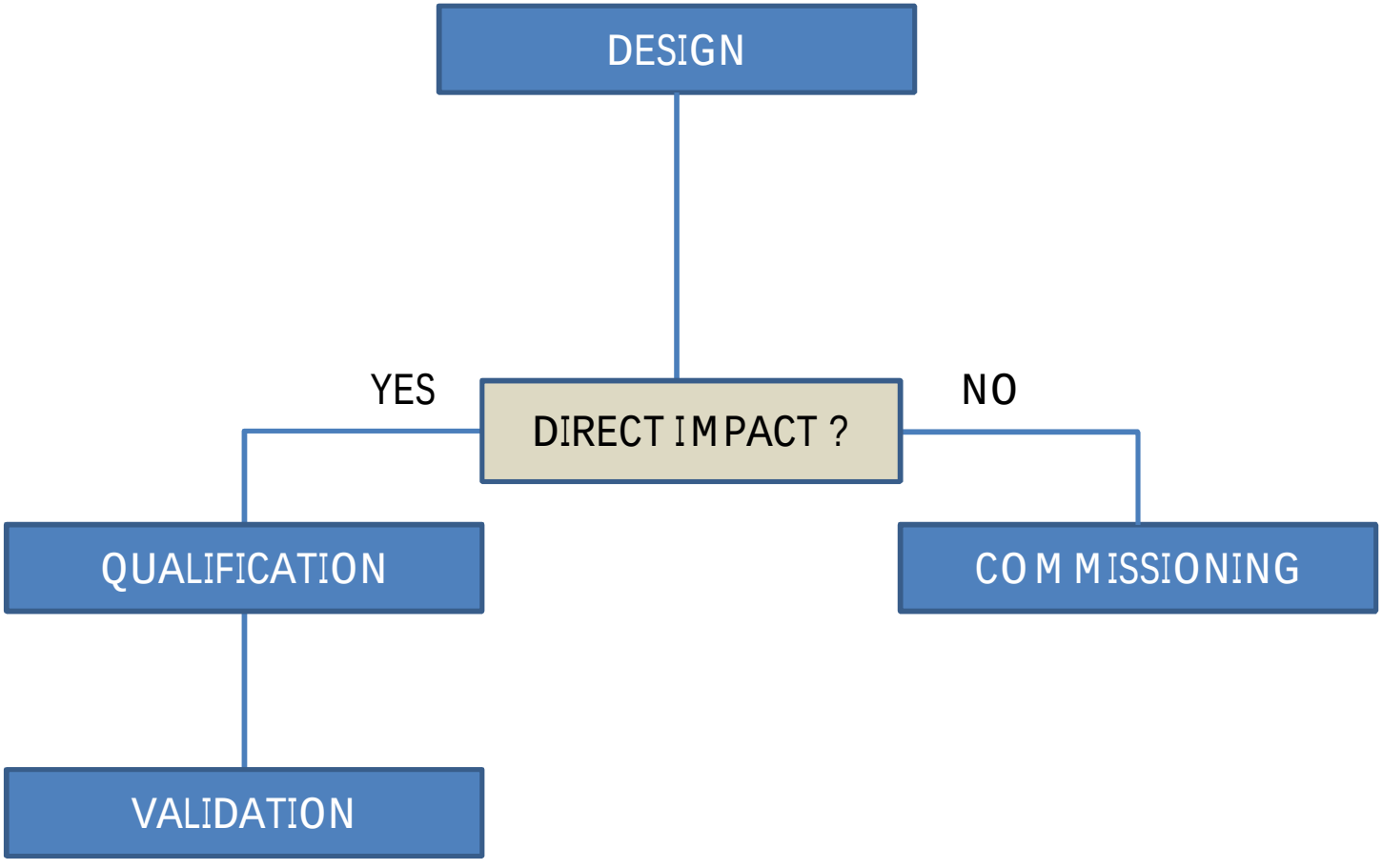
It must follow a PDCA rule.

NOT TO DO

Do not push Risk Management beyond common sense you must

- Define an approach that is maintainable

- Scale the effort based on criticality and complexity


DESIGN
YES
DIRECT IMPACT ?
NO
QUALIFICATION
COMMISSIONING
VALIDATION

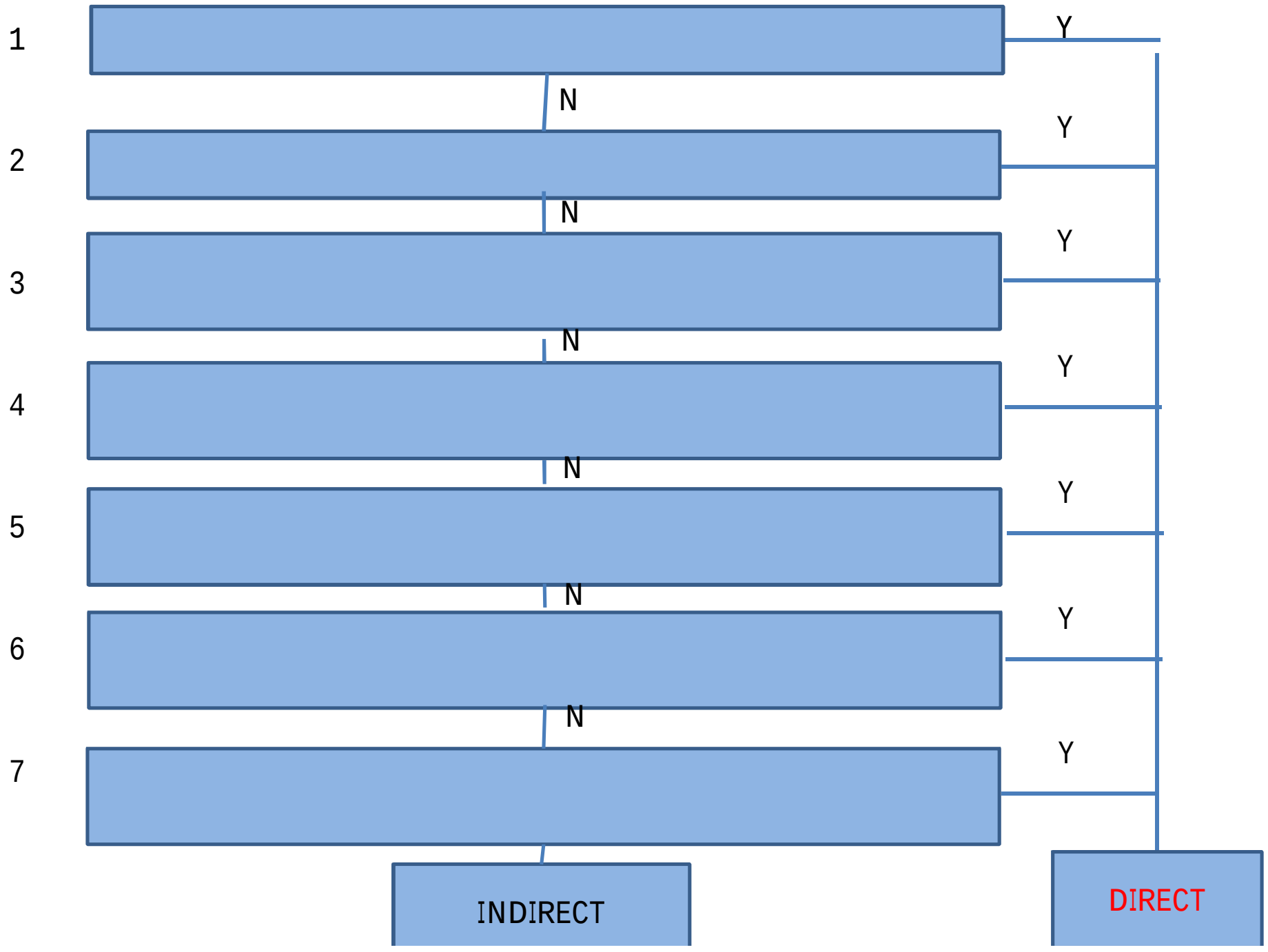
DIRECT IMPACT ?

How to determine that a system has a direct impact and therefore is Critical ?

Can you write down 5 questions to determine if the system has a direct impact ?

Example : Is the system in contact with the product ?
(syringe)

15 minutes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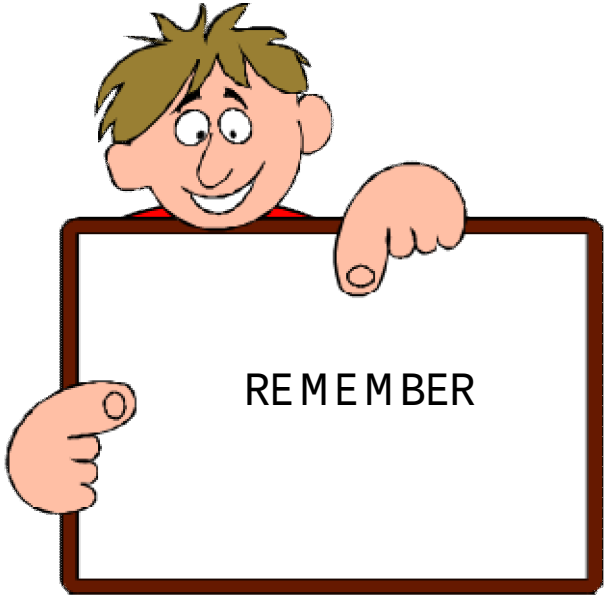
INDIRECT
DIRECT

- The table before is the rationale to explain why a process parameters has been identified as non-critical.

- A non critical parameter is also called a « general parameter »



DESIGN

1. IN LINE WITH URS
2. WILL DRIVE THE FUNCTIONAL SPECIFICATIONS.
3. WILL DEFINE THE OPERATIONAL RANGE
4. WILL DEFINE THE EXPECTED PERFORMANCES.
5. WILL INCLUDE THE RISK ASSESSMENT.
6. WILL INCLUDE THE MITIGATION OUTPUTS.
7. WILL INCLUDE THE STANDARDS.
8. WILL INCLUDE THE GOOD PRACTICES

QUALIFICATION

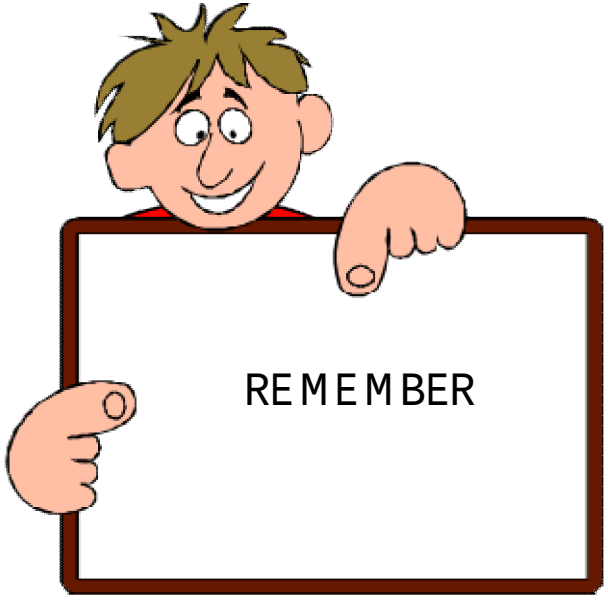
1. WILL BRING DOCUMENTED EVIDENCE THAT THE EQUIPMENT OR SYSTEM DELIVERED IS IN CONFORMITY WITH :
    1. URS
    2. SPECS
    3. STANDARDS
    4. INSTALLED CORRECTLY
    5. DOCUMENTED CORRECTLY
    6. INSPECTED AND TESTED CORRECTLY
    7. WILL INCLUDE TRAINING PLAN

VALIDATION

1. WILL BRING DOCUMENTED EVIDENCE THAT THE EQUIPMENT OR SYSTEM DELIVERED IS IN CONFORMITY WITH :
    1. EXPECTED PERFORMANCES.
    2. EXPECTED REGULATORY CONSTRAINS.
    3. SAFE AND PREDICTIBLE.
    4. ACCEPTANCE CRITERIA
    5. INTEGER DURING ALL THE LIFE CYCLE

Installation qualification

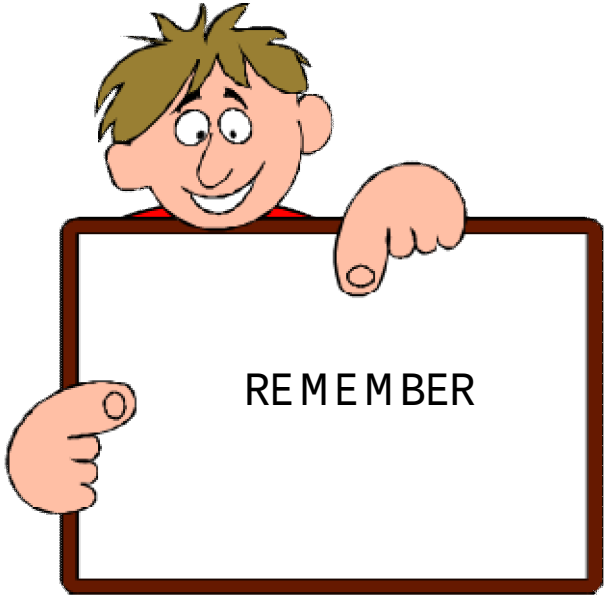
- IQ : Process of obtaining and documenting evidence that the equipment has been provided and installed in accordance with its specifications and is operating in accordance with the process.



Periodic re Validation

- Even If a system is suitably designed, qualified, operated and maintained, it needs to be re evaluated periodically and eventually re-validated.

- Annual review
- Re validation program



COMMISSIONING

1. WILL BRING DOCUMENTED EVIDENCE THAT THE EQUIPMENT OR SYSTEM DELIVERED IS IN CONFORMITY WITH :
   1. PURCHASE ORDER
   2. URS
   3. SPECIFICATIONS

Conclusion

- ICH Q10 is not intended to create any new expectations beyond current regulatory requirements. Consequently, the content of ICH Q10 that is additional to current regional GMP requirements is optional.

- The elements of ICH Q10 should be applied in a manner that is appropriate and proportionate to each of the product lifecycle stages, recognising the differences among, and the different goals of each stage