

PHARMACEUTICAL  
CONSULTANCY  
SERVICES

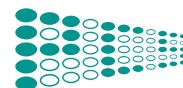
# Process Validation (based on FDA guide)

# PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

## **Process Validation and Drug Quality**

Effective process validation contributes significantly to assuring drug quality. The basic principle of quality assurance is that a drug should be produced that is fit for its intended use. This principle incorporates the understanding that the following conditions exist:

- Quality, safety, and efficacy are designed or built into the product.
- Quality cannot be adequately assured merely by in-process and finished-product inspection or testing.
- Each step of a manufacturing process is controlled to assure that the finished product meets all quality attributes including specifications.

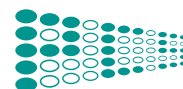


# PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

## Approach to Process Validation

*Process validation* is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product.

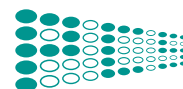
*Process validation* involves a series of activities taking place over the lifecycle of the product and process.



# PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

## Approach to Process Validation, ctd

- **Stage 1 – Process Design:** The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities.
- **Stage 2 – Process Qualification:** During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing.
- **Stage 3 – Continued Process Verification:** Ongoing assurance is gained during routine production that the process remains in a state of control.

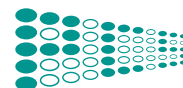


# PROCESS VALIDATION: GENERAL PRINCIPLES AND PRACTICES

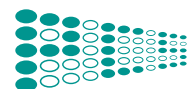
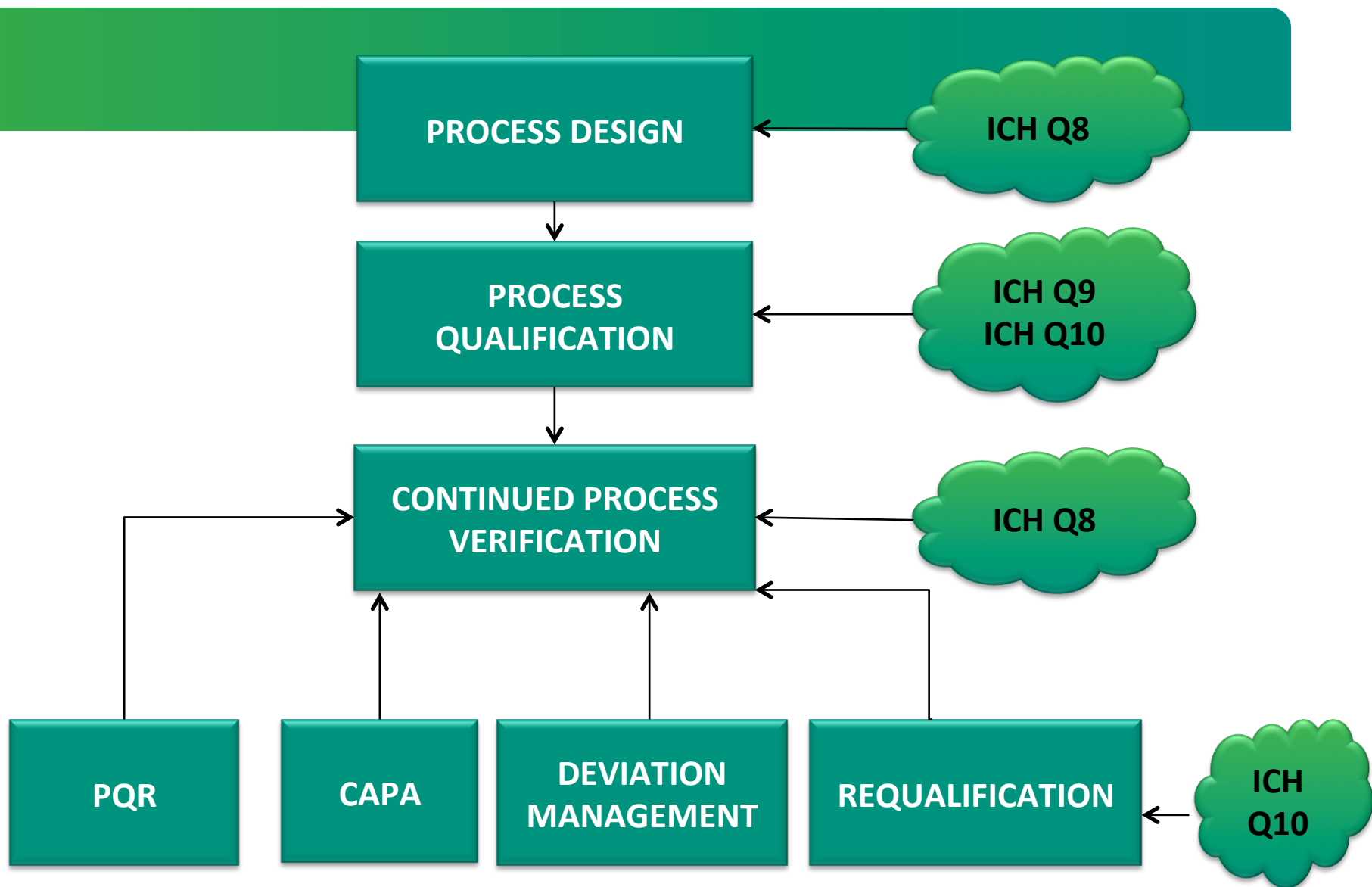
## Approach to Process Validation

A successful validation program depends upon information and knowledge from product and process development. This knowledge and understanding is the basis for establishing an approach to control of the manufacturing process that results in products with the desired quality attributes. Manufacturers should:

- Understand the sources of variation
- Detect the presence and degree of variation
- Understand the impact of variation on the process and ultimately on product attributes
- Control the variation in a manner commensurate with the risk it represents to the process and product







# DESIGN PHASE

## During the Design Phase

- Build to be robust....
  - QbD (Quality by Design)
  - DoE (Design of Experiments)Knowledge-building process, intermediates, product
- Development/Engineering of the Process
  - Block Flow Diagram (BFD)
  - Process Flow Diagrams (PFD)
  - Parameters, determine critical (CCP) and non-critical parameters

*Develop a definition of what is- and what is not critical*



# DESIGN PHASE

## During the Design Phase, *ctd.*

- Development/Engineering of Process

- Attributes, critical (CQA) and non-critical

*Quality Attributes: read the specification, it is advisable to develop for in-process, intermediates and product.*

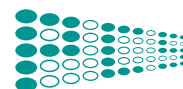
*The same problem applies here; it is very hard to determine what is critical and non-critical*

- Material Input: Qualified Vendors (!)

- Holding Times (!)

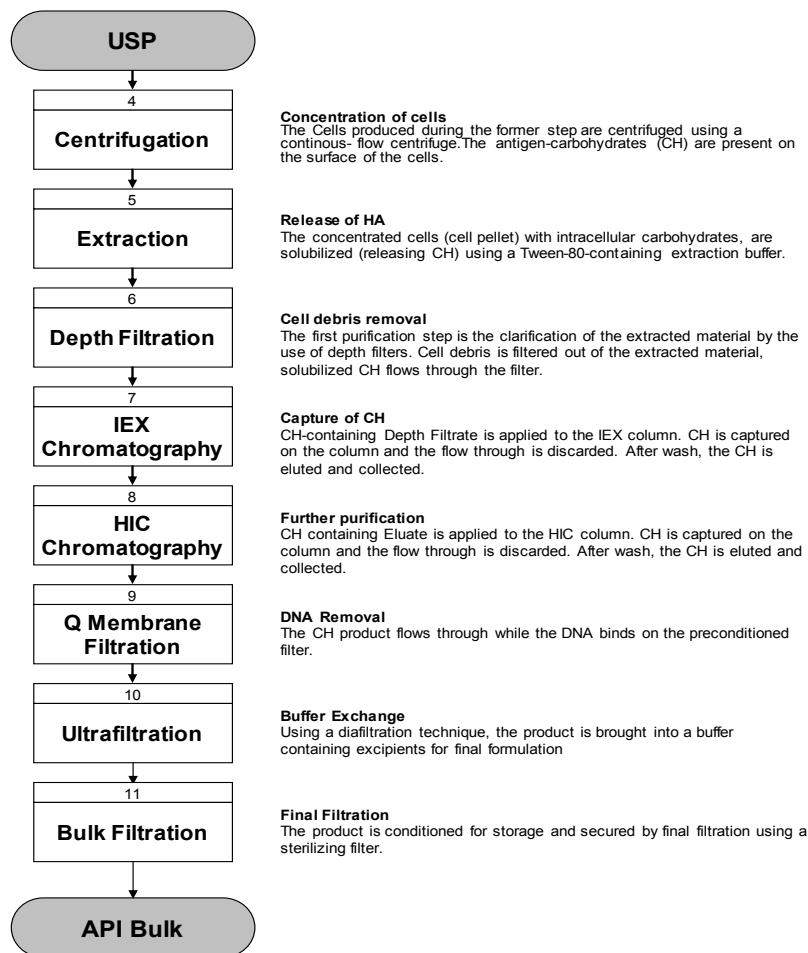
- Sampling plan: develop for use during the commercial phase.

*Advise: develop a process-training manual containing a process-description and an explanation of the rationale for the chosen Parameters and Attributes (specifications in-process/product).*

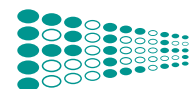
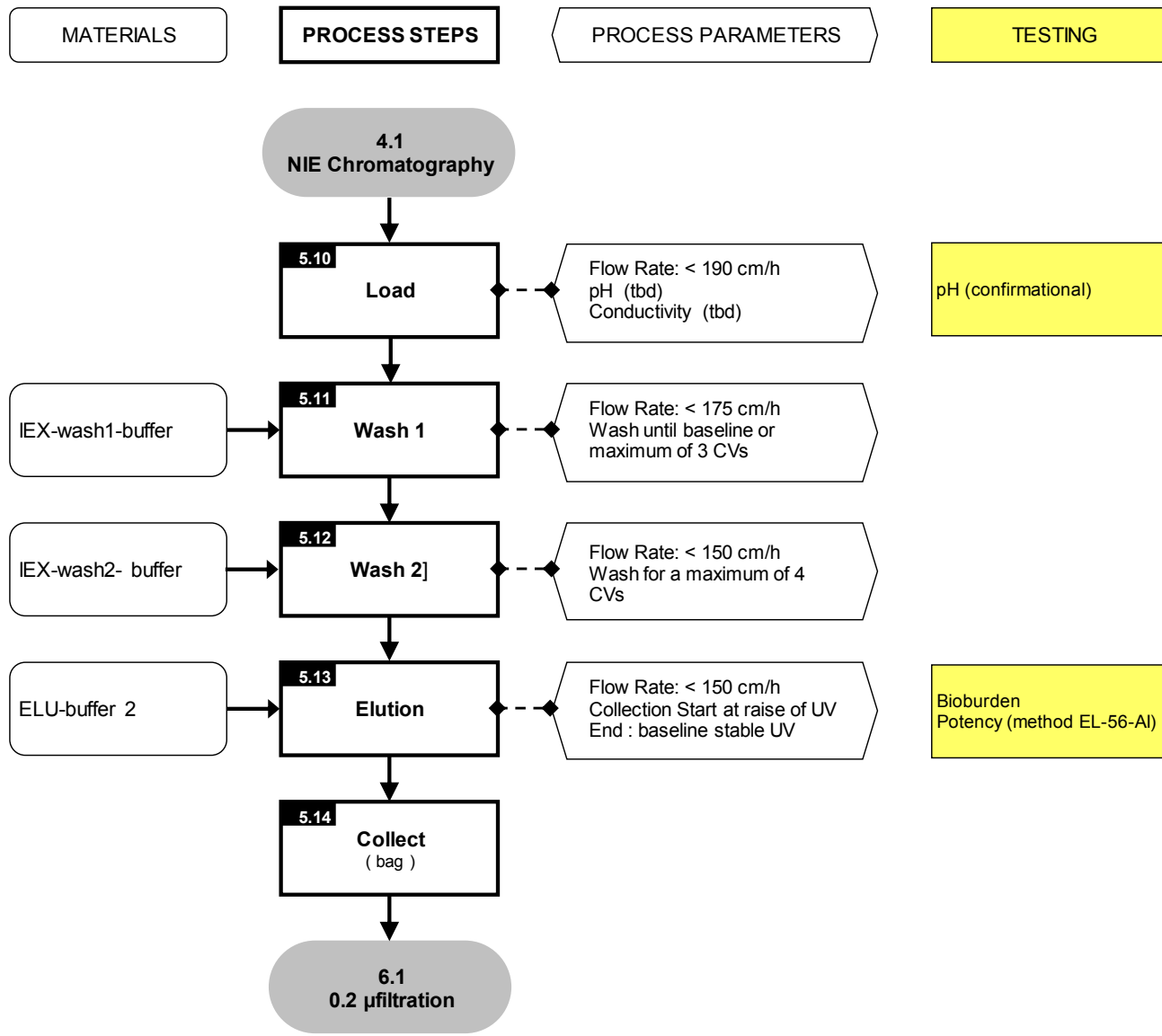




# BFD (EXAMPLE)



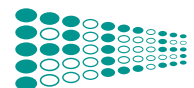
# PFD (EXAMPLE)



# DESIGN PHASE

## During the Design Phase, *ctd.*

- The final goal BEFORE the commercial phase has begun is to have process-robustness.  
*In other words: as few improvizations as possible when the product/process goes commercial.*
- Whereby the process is fully defined, after which training (knowledge-transfer) to operations can proceed at an optimal level.
- QA is indispensable for correctly and critically defining and recording process-definitions.

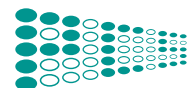


# PPQ PHASE

## PPQ (FDA-term)

- Process Performance Qualification preceded by Qualification of equipment, facilities, utilities, personnell etc.
- Defined test-functions to show process-robustness
- Number of batches (when does the PPQ-fase stop): rationale is present.
- Not in the guidelines but widely used: CpK

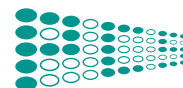
*However; in an older draft –late 90's- Annex 15 (EU) mentioned CpK.*



## STAGE 1: PROCESS DESIGN

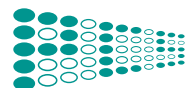
- Non-GMP phase of “Development” and “Engineering Runs”
- Small scale → pre-commercial scale
- Critical process steps, parameters and ranges defined
- Helpful tools: PFD
- Risk analysis techniques used (e.g. FMEA , HACCP)
- Process control strategy developed (IPCs, Intermediates, on line PAT)
- Final process defined

**General requirements of ICH Q8 apply**



## STAGE 2: PROCESS QUALIFICATION

- Qualification of facilities (IQ/OQ prerequisite)
- Demonstrate that commercial manufacture performs as expected
- “Decision to begin commercial distribution should be supported by data from commercial-scale batches”
- “Not all process ranges need be explored” during process validation
- Process validation has “higher level of sampling, testing and scrutiny”
- Performed according to classical protocol/report system
- 3 batches is usual but may not be appropriate (!)

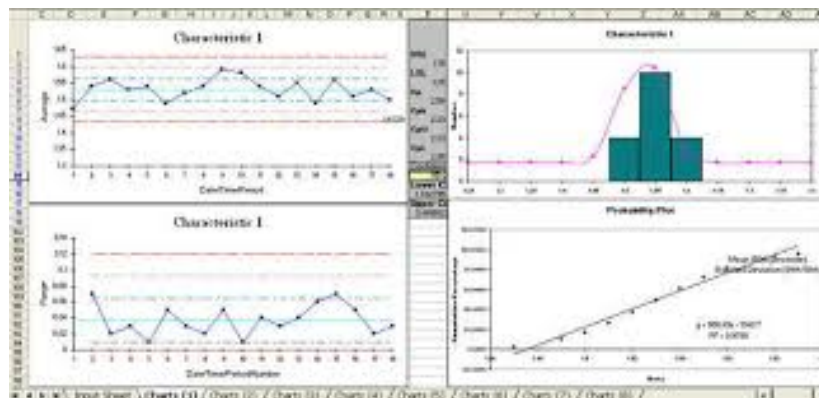




# STAGE 3 CPV PHASE

## Continued Process Verification (FDA term)

- After formal closure of the initial process-validation activities, process should be monitored (Process-vigilance) for trends and process-improvements.
- Data-points, depending on the process and circumstances
- Such as (examples, not limited to):
  - *CpK's*
  - *Data-mining*
  - *Statistics*
  - *OOT's (Out of Trends)*
  - *Reporting*
  - *Metrics / Quality Reporting*
  - *Management Review*



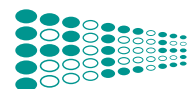
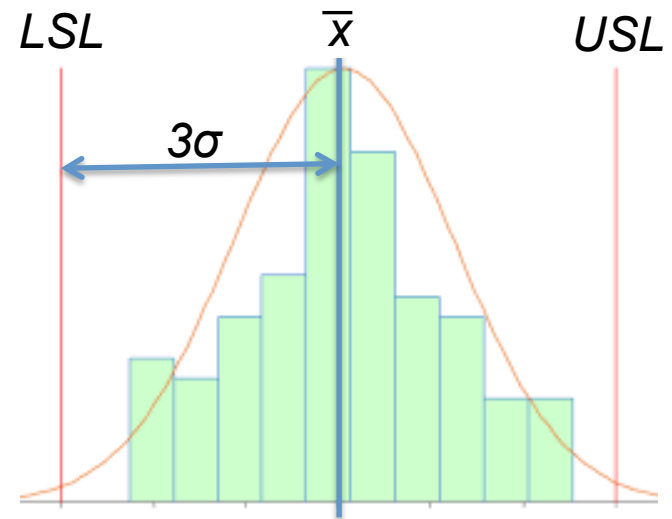
# STAGE 3 CPV PHASE

## Continued Process Verification (FDA term)

- Not in the guidelines but widely used: CpK

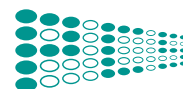
$$CpK \leq 1 ; \quad 1 < CpK < 1,33 ; \quad CpK \geq 1,33$$

$$Cpk = \min \left\{ \frac{USL - \bar{x}}{3\sigma}, \frac{\bar{x} - LSL}{3\sigma} \right\}$$



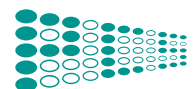
## STAGE 3: CPV

- “Continual assurance” that process is in a state of control
- Process operates within the “validated state”
- Adherence to cGMP requirements to detect “undesired process variability”
- “Ongoing programme to collect and analyse product and process data must be established” (e.g. APQR)
- Use of statistical trend analysis “recommended”
- “Quality Unit should review this information”
- Higher level of sampling and testing should continue during initial phase of commercial manufacture (concurrent validation)

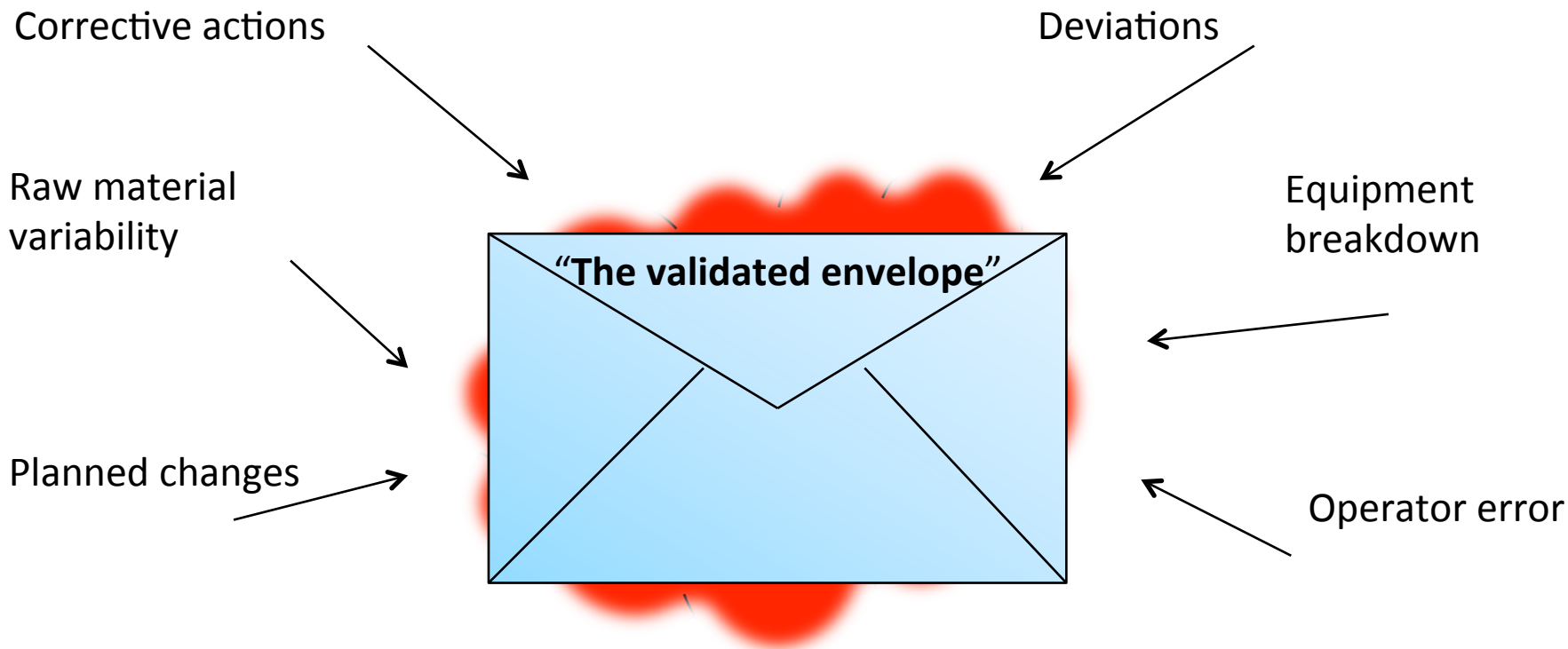


## STAGE 3: CONTINUED PROCESS VERIFICATION

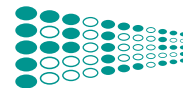
- Timely assessment of defects, complaints, OOS, yields, batch records etc.
- “Production line operators and quality unit staff to provide feedback on process performance”
- “Recommend quality unit met periodically with production staff to evaluate data”
- Data used to feed a CAPA system after full evaluation
- Changes driven by CPA to be implemented via change control system
- Significant changes may result in new process design, process qualification (and licensing)
- Remark (not in hand-out) check product performance, recalls, complaints and the more, to assure that you didn’t “missed” something in your IPC/QC -testing



# THE VALIDATED ENVELOPE

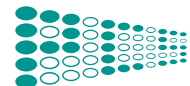


**How far can the process move out of the validated envelope before it is no longer valid?**



# RISK BASED DECISION MAKING

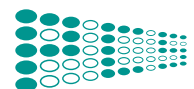
- All non-validated conditions represent a potential risk to product (and regulatory compliance) and should be avoided
- Wherever possible, the validated envelope should be wide enough to include anticipated conditions (e.g. largest and smallest batch sizes, processing times, conditions, etc.)
- Certain failure modes (e.g. power loss) can be identified using risk assessment tools (e.g. FMEA) and can be prospectively validated.
- Validation cannot foresee all situations that may arise
- Decision on non-validated situations will be made based upon risk assessment principles (ICH Q9)
- Decisions to be made include:
  - Impact of event on product quality
  - Impact of event on other products/batches/regulatory impact assessment
  - Need for additional supporting data (e.g. stability)
  - Corrective actions
  - Preventative actions





# RISK BASED DECISION MAKING: CRITICAL SUCCESS FACTORS

- Access to all relevant data (current event, historical situation trends)
- Appropriate subject matter experts (Production, QC, Engineering)
- Use of standardised risk assessment methodology to ensure impact is correctly defined
- Use of standardised investigational tools to ensure plausible root cause analysis and definition of most appropriate CAPAs
- Thorough documentation of decision-making process, including justification for actions taken
- Avoidance of “box ticking” attitude and “quick fixes”

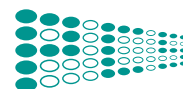


# EQUIPMENT QUALIFICATION PREREQUISITE FOR PROCESS VALIDATION



# GENERAL INTERNATIONAL REQUIREMENTS

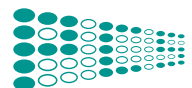
- All utilities that could impact on product quality (e.g. steam, gases, compressed air, HVAC) should be qualified ...
- Where water used in the process is treated by the manufacturer ... the treatment process should be validated.
- Production equipment should only be used within its qualified operating range
- A set of current drawing should be maintained for equipment and critical installations
- GMP related computerised systems should be validated.  
The depth and scope of validation depends on the diversity, complexity and criticality of the computerised application.



# GENERAL INTERNATIONAL REQUIREMENTS

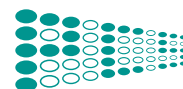
- Appropriate installation qualification and operational qualification should demonstrate the suitability of computer hardware and software to perform assigned tasks.
- The company's overall policy, intentions and approach to validation should be documented (VMP)
- Before starting process validation, appropriate qualification of critical equipment should be completed...

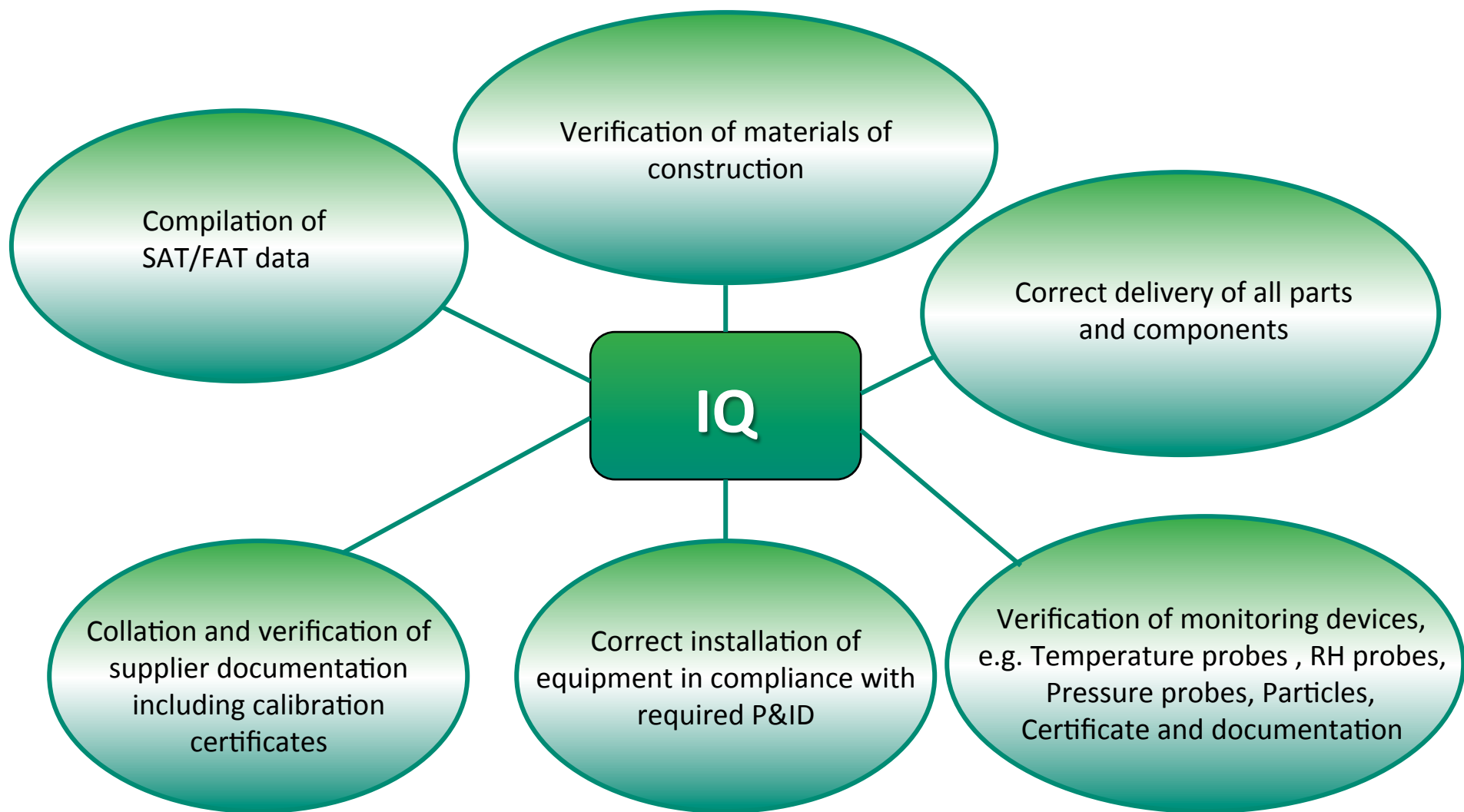
## THE CURRENT IQ/OQ PARADIGM



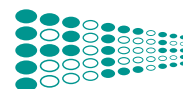
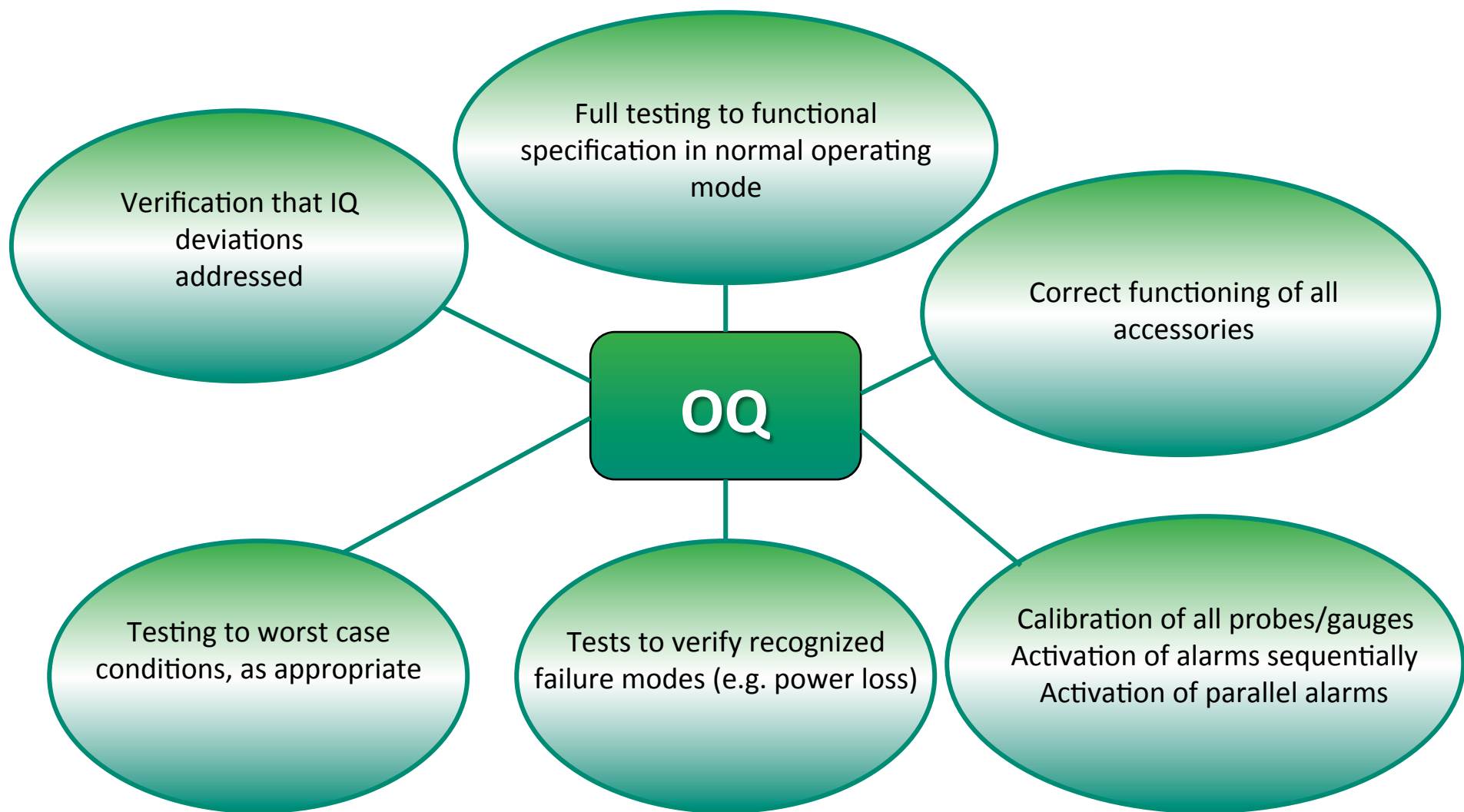
# DESIGN QUALIFICATION

- A qualification milestone in which the URS and the Functional Specifications are formally approved.
- Change Control applies after DQ to manage changing requirements or functional specifications as the project proceeds
- DQ forms the basis for all following qualifications (IQ/OQ) and validation (PQ) requirements
- DQ often regarded as the first official GMP document (in conjunction with URS).



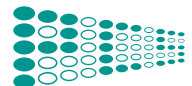






## Specification, Design and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment

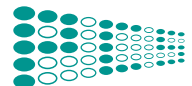
August 2007



# BACKGROUND TO ASTM E 2500 - 07

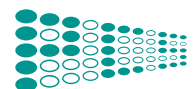
1. Current qualification / validation approach is burdensome (DQ/IQ/OQ/PQ)
2. No focus on risks, more on formality
3. Little consideration of patient risks
4. Often no recognition of supplier documentation
5. Duplication of effort

**CURRENT PARADIGM IS NOT “RISK BASED”**



# ASTM E 2500 – 07 KEY FEATURES – 1 –

1. Supported (and implemented/used) by FDA / EMA
2. Focus on “Good Engineering Practices”
3. Use of Risk Management, Design Review, Change Control
4. Qualification based on knowledge of product and process (less equipment focus)
5. DQ/IQ/OQ/PQ not required as a formality
6. More emphasis on “Subject Matter Experts”, less on QA



## ASTM E 2500 – 07 KEY FEATURES – 2 –

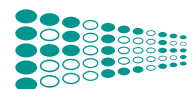
### 7. QA focus on:

- 7. - URS
- 8. - Project Quality Plan (Verification Plan)
- 9. - Risk assessments
- 10. - Review of non-conformances
- 11. - Approval of Performance Test

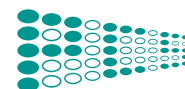
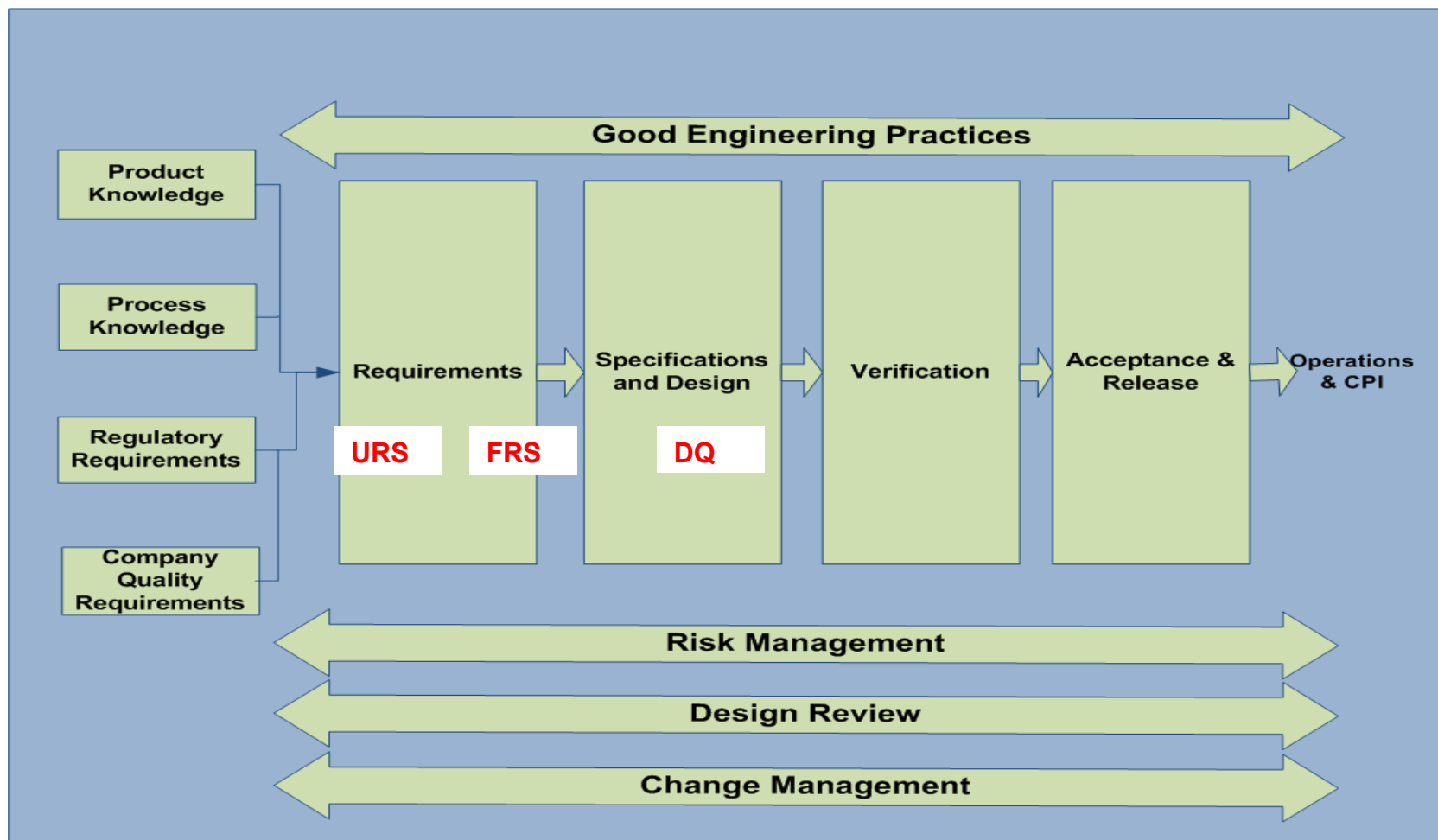
### 8. Change Control starts from Performance Test

### 9. “Verification Plan” replaces DQ/IQ/OQ/PQ Paradigm

**ISPE COMMISSIONING / QUALIFICATION GUIDELINE  
REVISED AND ALIGNED WITH ASTM E 2500**

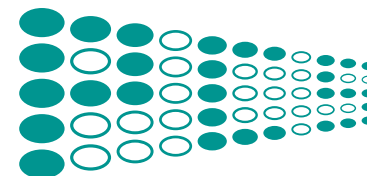


# ASTM 25007





# THANK YOU FOR YOU ATTENTION



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