Best Practices Commissioning & Validation

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Best Practices Commissioning & Validation

Facilitating Quicker Pharmaceutical Project Delivery

Agenda

This presentation will discuss the current trends in Commissioning and Qualification (C&Q), it will cover

- Review of current (FDA and EU) regulatory environment and trends
- Master Planning Commissioning and Qualification
- Best Practice Commissioning and Start-up
- Risk Assessment to Reduce Qualification Load
- Leveraging and Utilising Vendor Testing to maximum impact
- Change control strategy across the project lifecycle

Establishing the Regulatory Basis

Facilitating Quicker Pharmaceutical Project Delivery

Regulatory Drivers

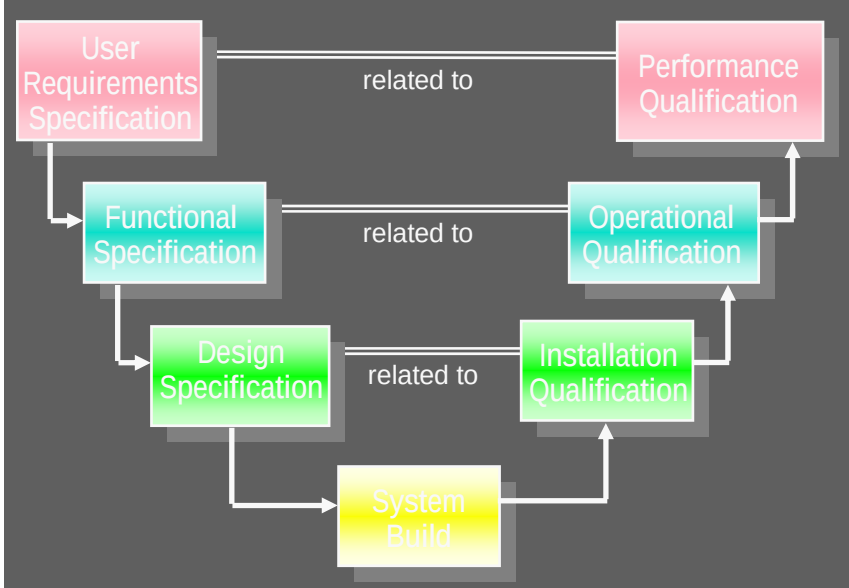
- 21st Century cGMP Initiative
- PIC/S Guidance
- EU Volume 4

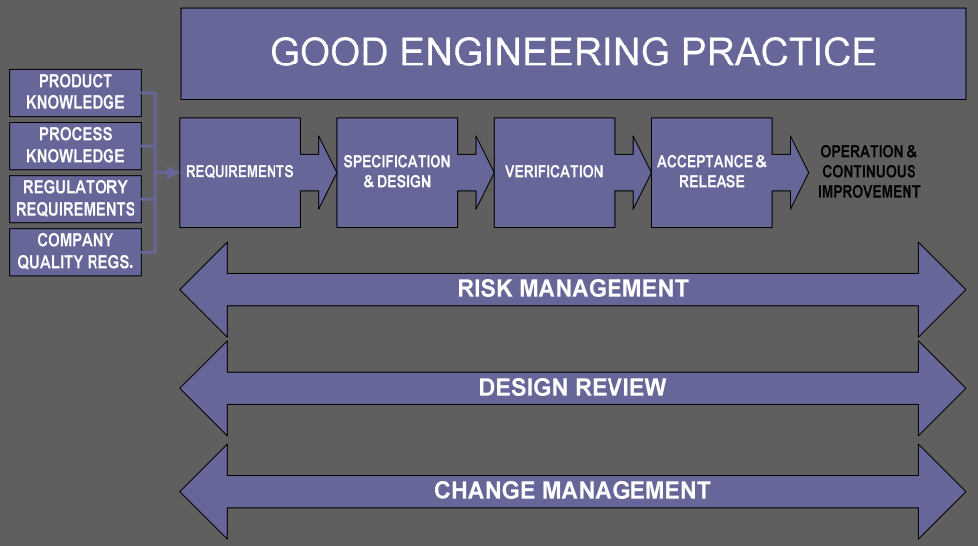
Other Drivers

- ISPE Product Quality Lifecycle Implementation (PQLI) Initiative
  - Practical Implementation of ICH Guidance and Quality by Design
- ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment
- GAMP 5 Guidance
- ISPE GEP best practise guide
- FDA draft PV guidance 2008
- ISPE Baseline Guide 12 Draft Verification guide
- FDA: Quality Systems Approach to Pharmaceutical cGMP Regulations – 2006
- EU Annex 20, Quality Risk Management – March 2008
- ICH Q8 Pharmaceutical Development - Nov 2005
- ICH Q10 – Quality Systems – June 2008

Beginning with the End in Mind

Traditional ‘V’ Model or Risk Based Verification





Back to the Basics – Why Qualify?

FDA regulatory perspective

- Process validation is required in both general and specific terms, by the Current Good Manufacturing Practice Regulation for Finished Pharmaceuticals, 21 CFR Parts 210 and 211.

- § 211.210 Sampling and testing of in-process materials and drug products.

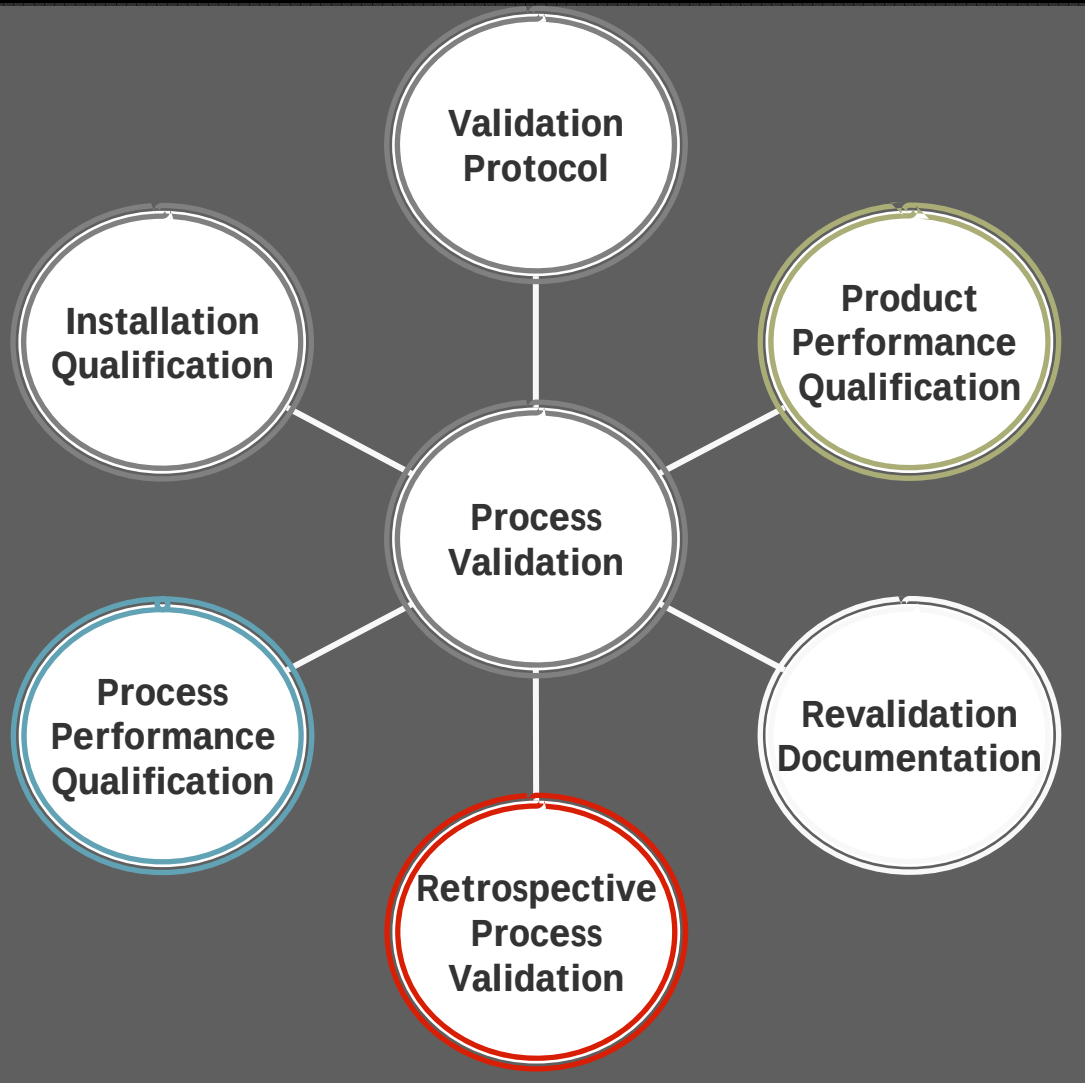
  (a) To assure batch uniformity and integrity of drug products, written procedures shall be established and followed that describe the in-process controls, and tests, or examinations to be conducted on appropriate samples of in-process materials of each batch.

  Such control procedures shall be established to monitor the output and to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

Qualification – The "old way"

"Process validation is *establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes*".

U.S. Food and Drug Administration. Guideline on General Principles of Process Validation, p 3: May 1987.



Back to the Basics – Why Qualify?
EU Regulatory Perspective

"It is a requirement of GMP that manufacturers identify what validation work is needed to *prove control of critical aspects* of their particular operations. Significant changes to facilities, the equipment and the processes, *which may affect the quality of the product,* should be validated. A *risk assessment approach* should be used to determine scope and extent of validation."

EU Guide to GMP Vol 4, annex 15 – Qualification and Validation- Issue Sept 2001

Activities are designated as:

- DQ ("First element …could be DQ")
- IQ
- OQ
- PQ

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Overarching Philosophy

- The overarching philosophy articulated in both the CGMP regulations *and* in robust modern quality systems is:
  - Quality should be built into the product, and testing alone cannot be relied on to ensure product quality

FDA Guidance for Industry Sept 2004
'Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations'

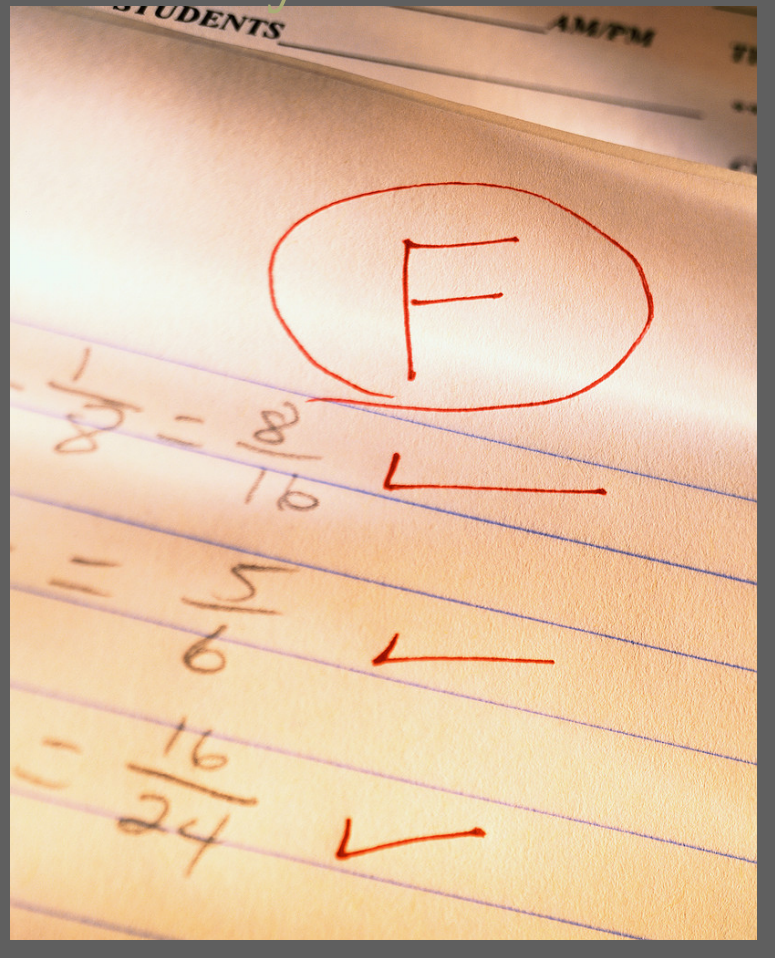
What Next C&Q ---------- Verification ?

Facilitating Quicker Pharmaceutical Project Delivery

Qualification Results

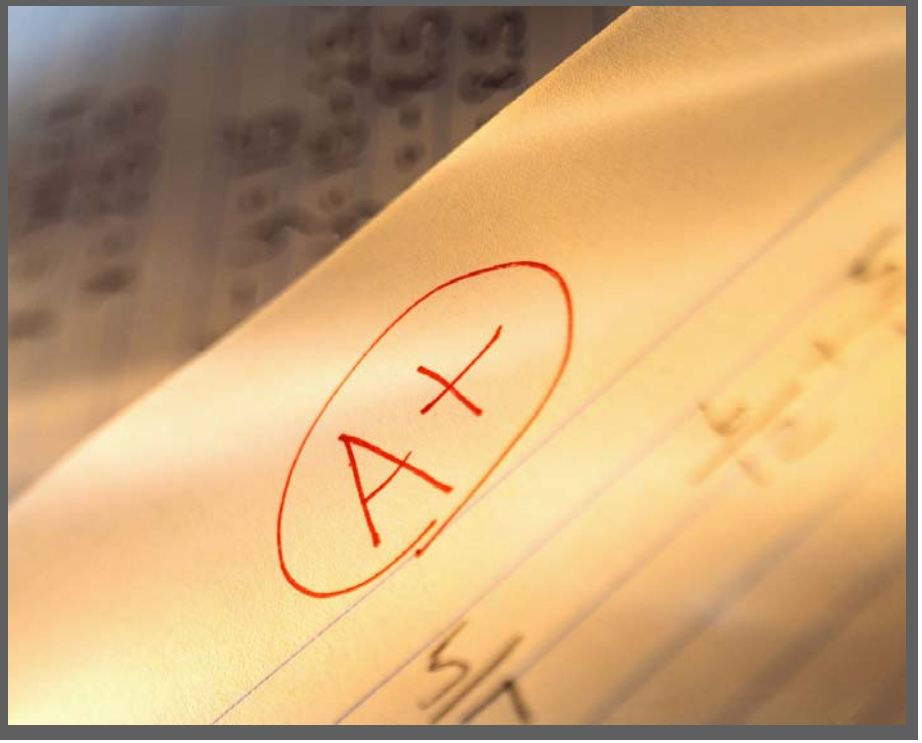
- The old way:
  - Documentation focused
  - Poor Scope Definition
  - Late Involvement of QA
  - Poor Commissioning Programmes
  - Commissioning running on into Qualification effort

Efficiency:

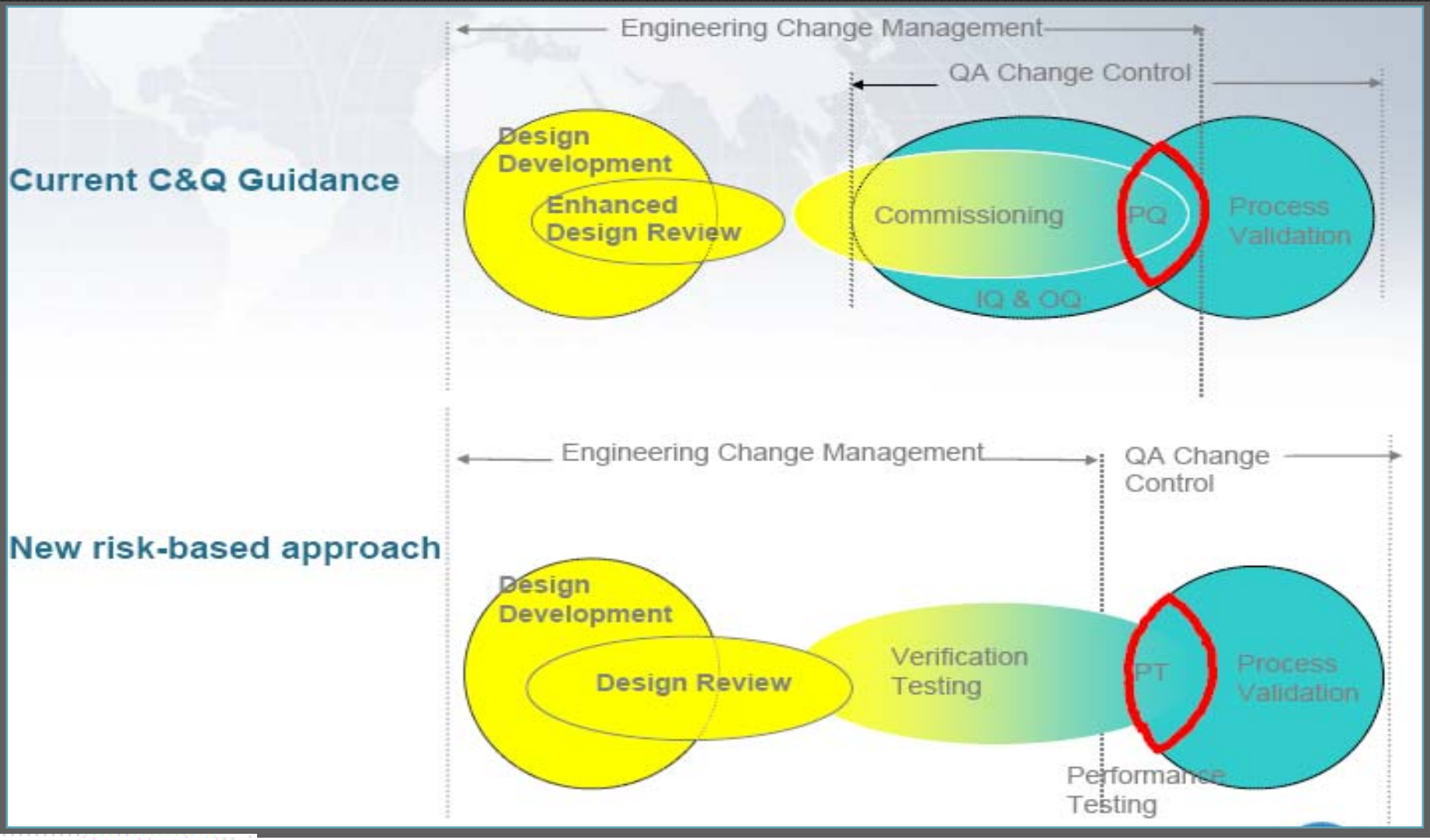


The New Way

- The old way:
  - Regulatory environment and industry is ready for change
  - Verification focus based on science and risk through Process User Requirements
    - CQA, CPP's
  - Risk Assessment confirms appropriate risk mitigation measures identified, used through the lifecycle
  - Project is RFT and C&Q is streamlined under the ASTM guidance



Old Vs New


Current C&Q Guidance
Engineering Change Management
QA Change Control
Design Development
Enhanced Design Review
Commissioning
PQ
Process Validation
IQ & OQ
New risk-based approach
Engineering Change Management
QA Change Control
Design Development
Design Review
Verification Testing
PT
Process Validation
Performance Testing

How ?

- Use of the 8 ASTM principles coupled with:
  - Integrated Lifecycle
  - Integrated Team
  - Integrated Design
  - Integrated Procurement
  - Integrated Scheduling
  - Integrated Construction/ Fabrication
  - Integrated Field Engineering
  - Integrated Change Management
  - Integrated Handover

ASTM E2500-07

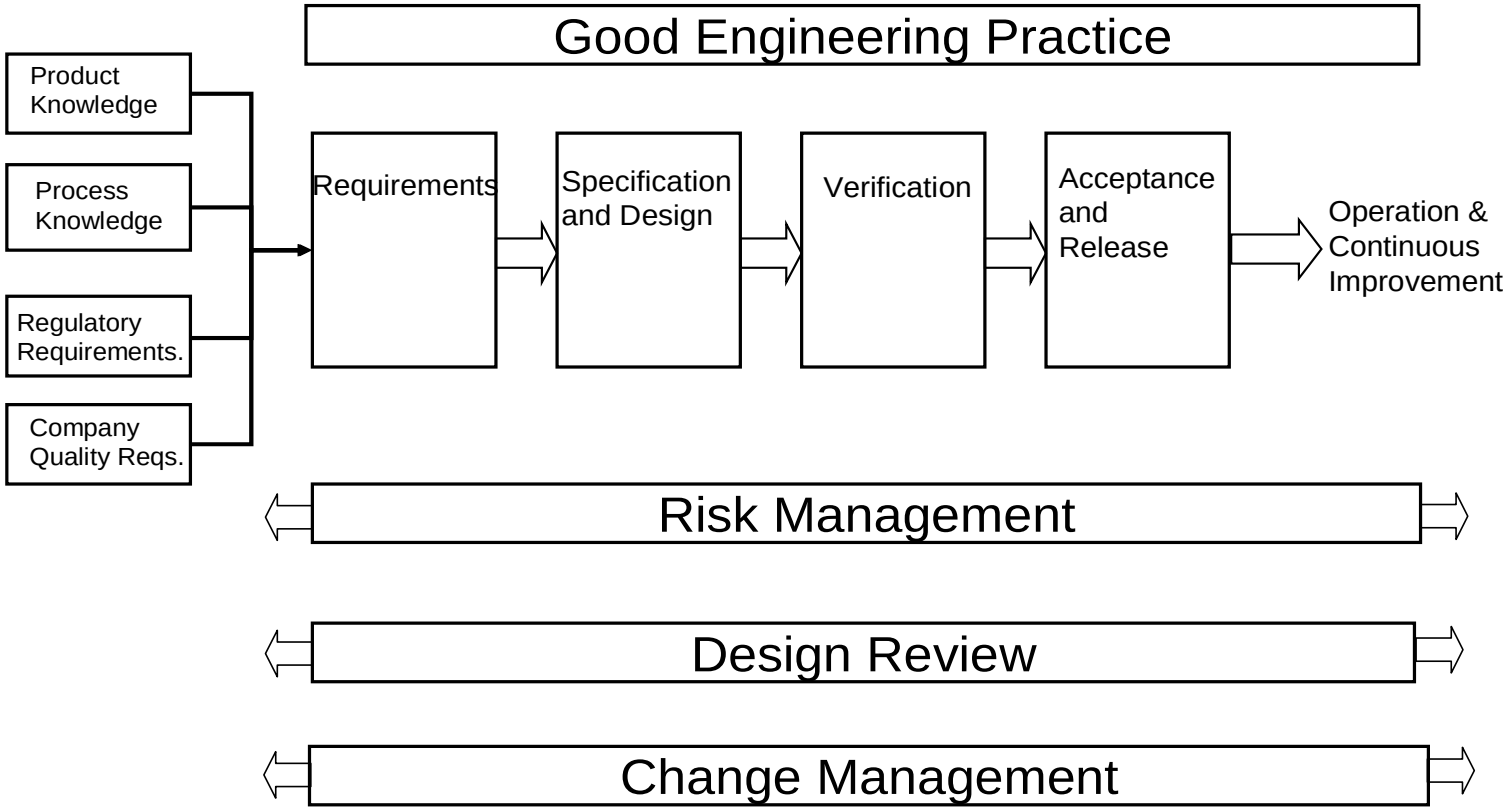


Figure 1 – The Specification, Design, and Verification Process

4 x 4 Step Process

1. Requirements Definition
2. Specification and Design
3. Verification
4. Acceptance and Release

1. Good Engineering Practice
2. Risk Management
3. Design Reviews
4. Change Management

applied throughout the process.

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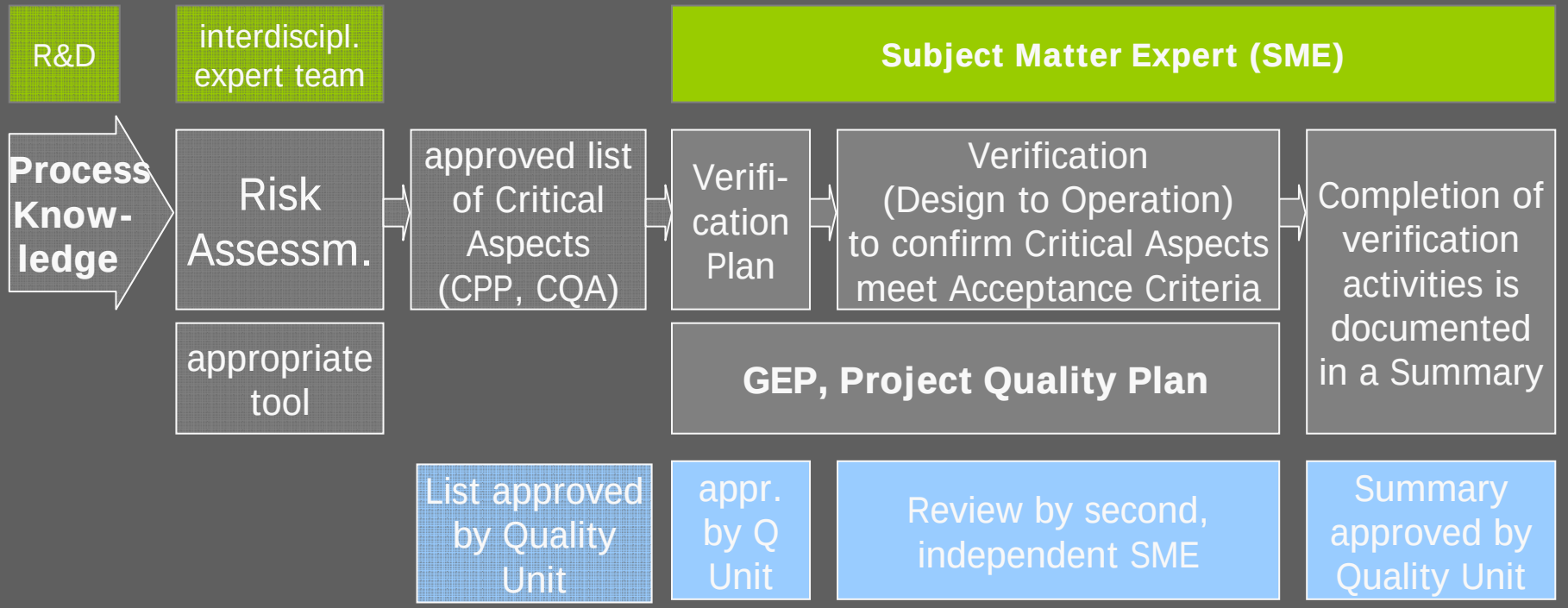
Verification Process Flow Chart



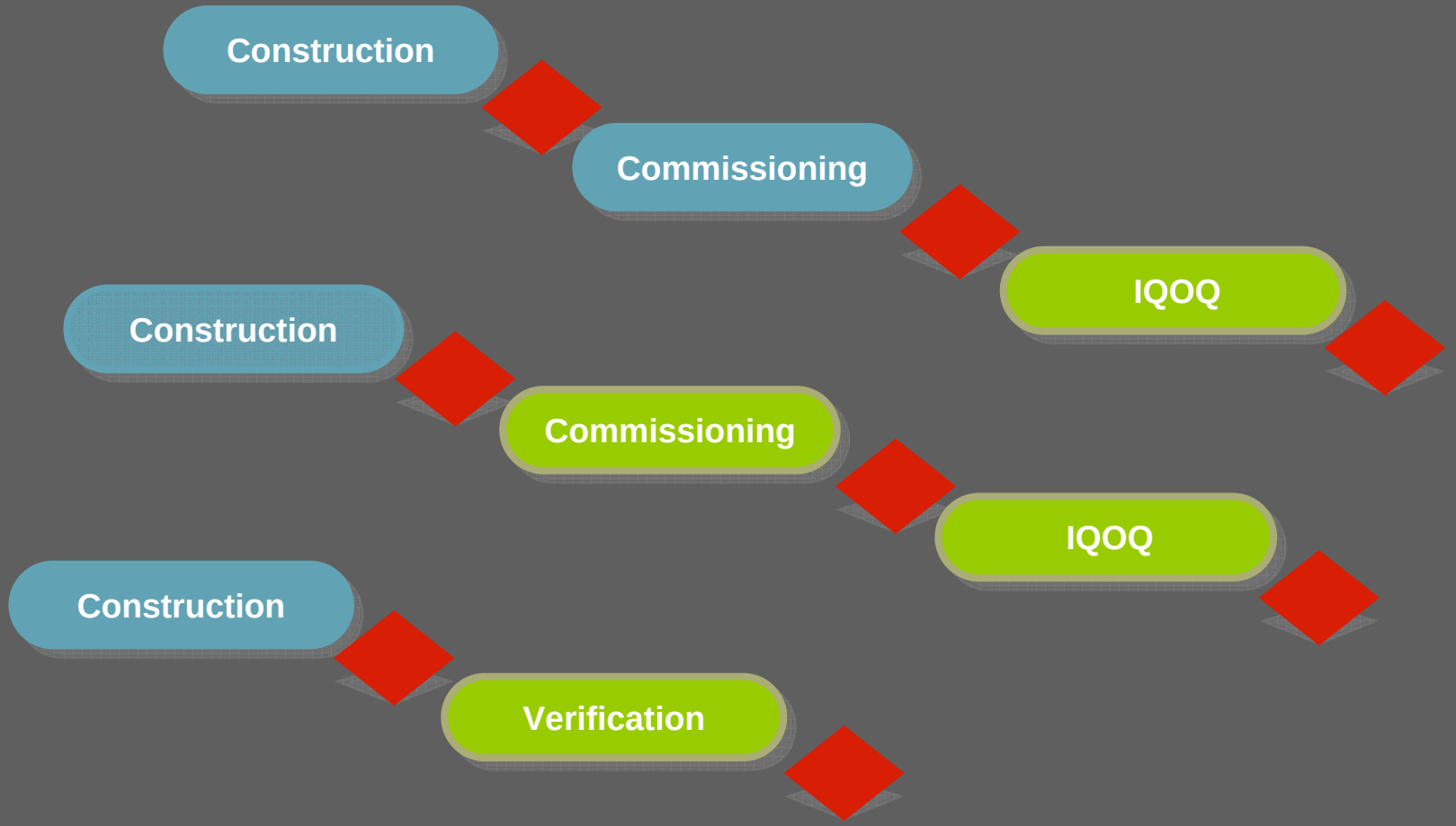
CPP: critical process parameter

CQA: critical quality attribute

What has to Change ?

- Adoption of the ASTM E2500-07 Standard Approved in July 2007
- Implement ICH Q8, Q9, Q10
- GEP best practise guide to be implemented
- In the meantime, we outline the applications of guidance and practices *currently* in use in an effort to demonstrate the most effective and successful implementation models
- Approval of the draft PV guide

Where to Next….ASTM ?



Steps to a successful Commissioning and Qualification Phase

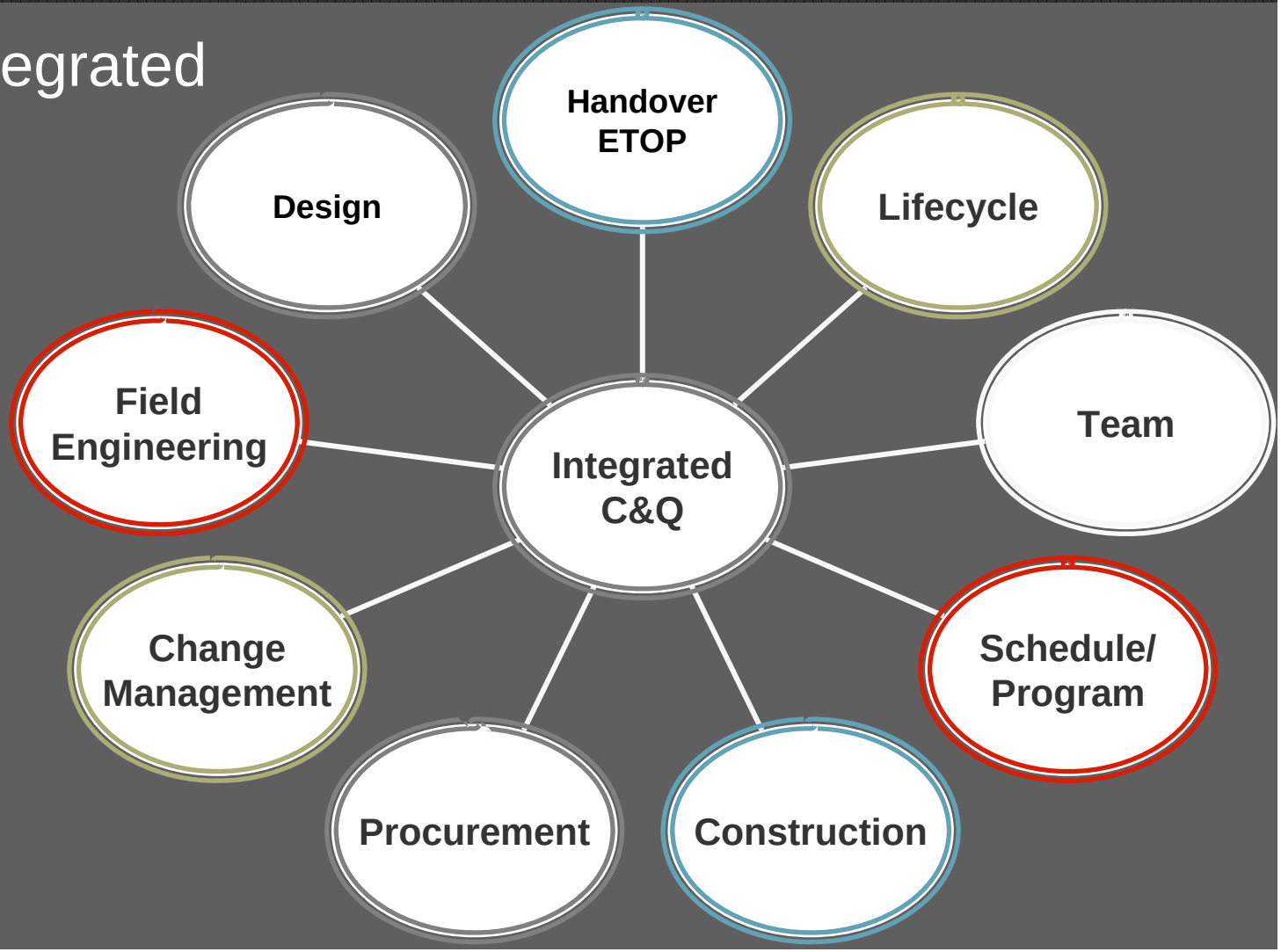
1. Master Planning Commissioning and Qualification
2. Best Practice Commissioning and Start-up
3. Risk Assessment to Reduce Qualification Load.
4. Leveraging and Utilising Vendor Testing to maximum impact.
5. Change control strategy across the project lifecycle.

1. Master Planning Commissioning and Qualification

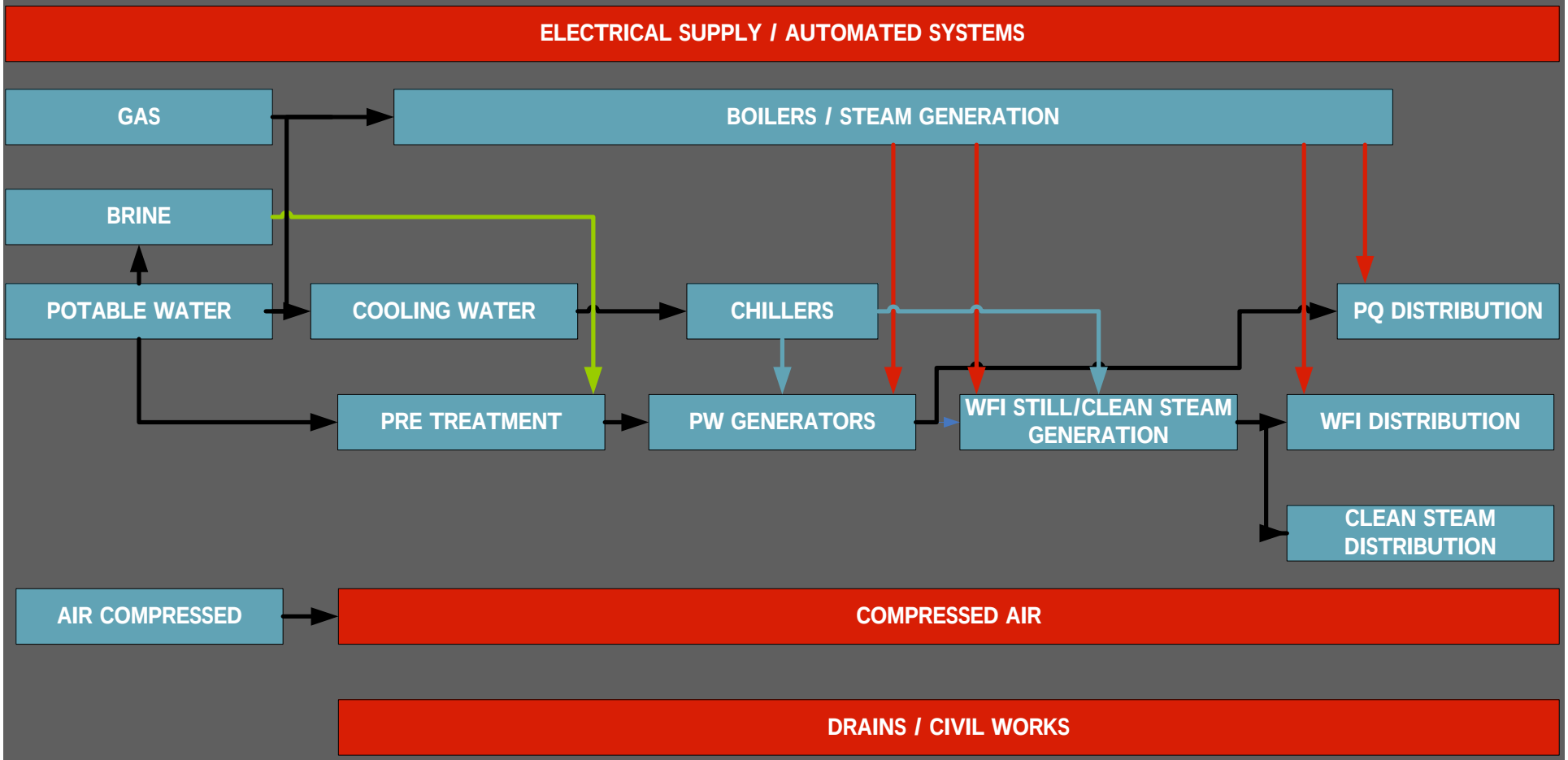
- Should be done regardless of the model (New/ Old)
- Define:
  - What testing is being performed in each PHASE
  - What testing is being done by each GROUP
- Tools:
  - Overall C&Q logic chart
  - Test Matrix
  - Integrated Project Schedule
  - Roles and Responsibility Matrix

1. Master Planning Commissioning and Qualification

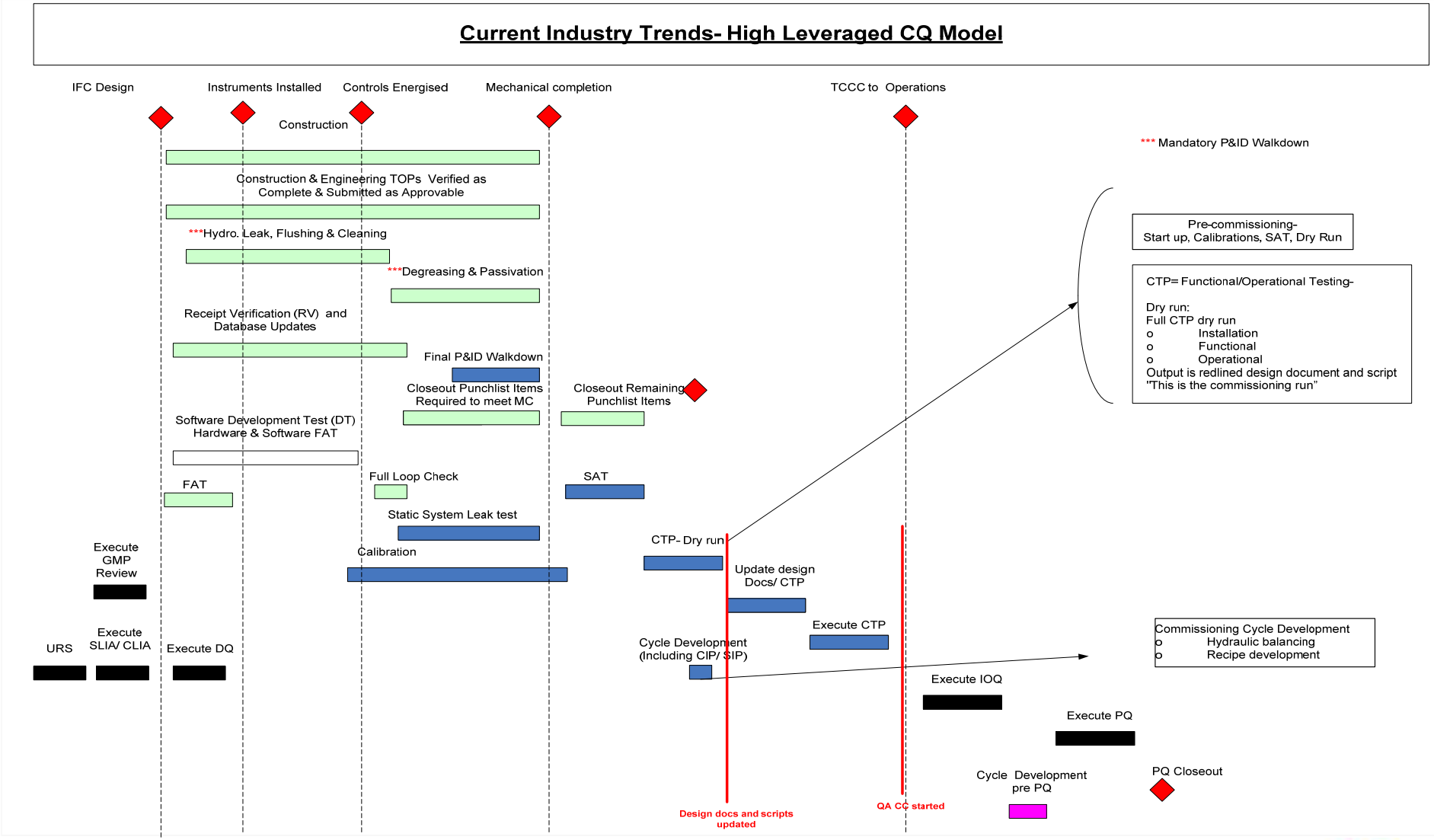
- Have an Integrated Approach



1. Master Planning Commissioning and Qualification
Planning Step 1: Start-Up Master Plan



1. Master Planning Commissioning and Qualification Planning Step 2: C&Q logic



1. Master Planning Commissioning and Qualification Planning Step 3: Test Master Plan

Test	FAT	Mechanical Completion	Commissioning / SAT	IQ	OQ	CQ/PQ/PV
Drawing Check						
Component Checks						
Documentation Checks						
Calibration						
Motor Rotation Check						
Handwired Interlock Checks						
Service / Leak Test						
Flushing and Blowdown						
Passivation / Cleaning						
Loop Checks						
Alarm Testing						
Back-Up and Restore						
Trending						
Security and Access Control						
Power Failure						
Functional Testing						
Alarm Testing						
Operational Testing Utilities						
Operational Testing Process						
Operational Testing Packaging						

An interactive planning session identify which test is done where and by whom

Also could add Receipt Verification etc

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1. Master Planning Commissioning and Qualification

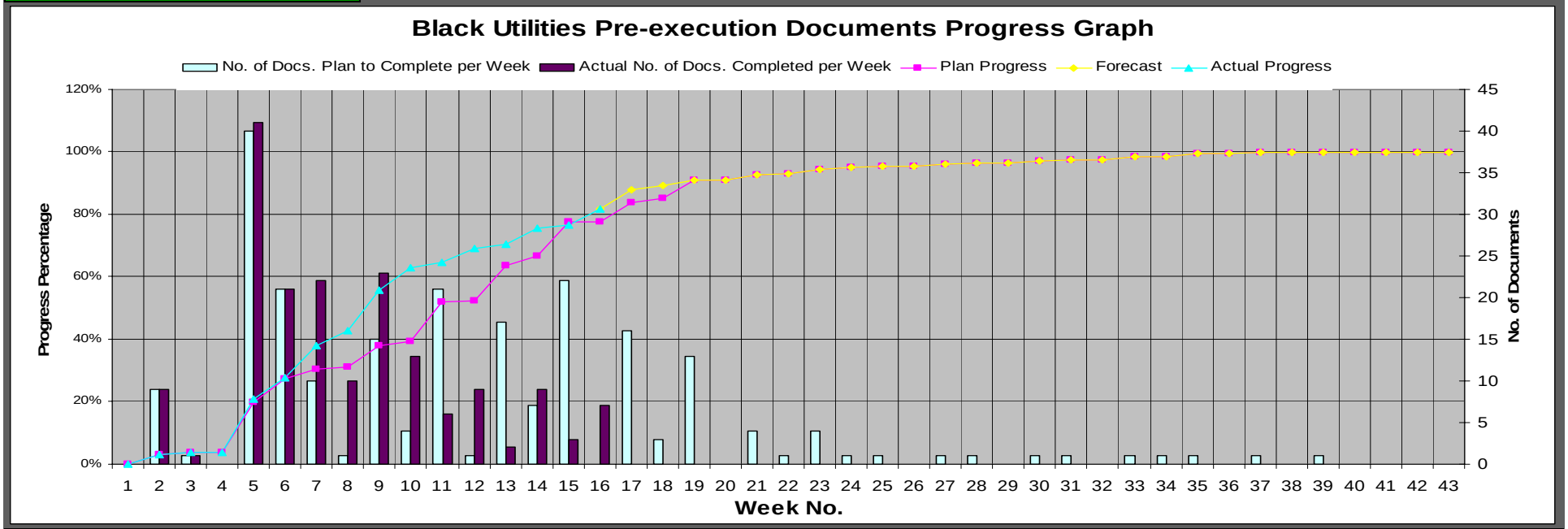
- Planning Step 4: Fully Integrated schedule
  - Start with a level 1 schedule from Design to regulatory approval
  - Construction Dates as Input date
  - Handover as Output date
  - Integrated Planning session essential
  - Feedback
- Planning Step 5: Roles and Responsibilities Matrix
  - For example LACTI Matrix
    - L = Leads
    - A = Approves
    - T = Tasked
    - C = Consults
    - I = Informed

1. Master Planning Commissioning and Qualification

- During project execution:
  - Monitor Schedule Progress
  - Carefully manage Commissioning and Qualification:
    - Track Progress
      - Upstream systems
      - Test Documents
      - Construction dates
      - Completion dates
    - Handover meetings to ensure smooth Handover:
      - From Construction
      - To User
    - Daily/ Weekly Toolbox talks
  - Have a clear reporting tool

1. Master Planning Commissioning and Qualification

Cut-off Date: 27-Jun-08



Week No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43
Week Ending	14/03/08	21/03/08	28/03/08	04/04/08	11/04/08	18/04/08	25/04/08	02/05/08	09/05/08	16/05/08	23/05/08	30/05/08	06/06/08	13/06/08	20/06/08	27/06/08	04/07/08	11/07/08	18/07/08	25/07/08	01/08/08	08/08/08	15/08/08	22/08/08	29/08/08	05/09/08	12/09/08	19/09/08	26/09/08	03/10/08	10/10/08	17/10/08	24/10/08	31/10/08	07/11/08	14/11/08	21/11/08	28/11/08	05/12/08	12/12/08	19/12/08	26/12/08	02/01/09
Plan Progress	0.00%	2.97%	3.74%	3.74%	20.00%	27.36%	30.48%	31.25%	37.96%	39.25%	51.89%	52.20%	63.43%	66.62%	77.54%	77.54%	83.85%	85.23%	91.08%	91.08%	92.77%	93.08%	94.31%	95.08%	95.38%	95.38%	96.15%	96.46%	96.46%	97.23%	97.54%	97.54%	98.31%	98.62%	99.38%	99.38%	99.69%	99.69%	100.00%	100.00%	100.00%	100.00%	100.00%
Actual Progress	0.00%	2.97%	3.74%	3.74%	20.77%	27.67%	37.78%	42.84%	55.67%	62.90%	64.75%	68.90%	70.44%	75.52%	76.44%	81.82%																													
Variance (+ -)	0.00%	0.00%	0.00%	0.00%	0.77%	0.31%	7.30%	11.58%	17.71%	23.65%	12.86%	16.70%	7.01%	8.90%	-1.10%	4.29%																											
Forecast																81.82%	87.85%	89.23%	91.08%	91.08%	92.77%	93.08%	94.31%	95.08%	95.38%	95.38%	96.15%	96.46%	96.46%	97.23%	97.54%	97.54%	98.31%	98.62%	99.38%	99.38%	99.69%	99.69%	100.00%	100.00%	100.00%	100.00%	100.00%
No. of Docs. Plan to Complete per Week	0	9	1	0	40	21	10	1	15	4	21	1	17	7	22	0	16	3	13	0	4	1	4	1	1	0	1	1	0	1	1	0	1	1	1	0	1	0	1	0	0	0	0
Actual No. of Docs. Completed per Week	0	9	1	0	41	21	22	10	23	13	6	9	2	9	3	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Remaining No. of Documents to Complete	221	212	211	211	170	149	127	117	94	81	75	66	64	55	52	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45	45

2. Best Practice Commissioning and Start-Up

The key to effective Commissioning and start-up is GEP

- Definition of GEP:
  - "*Established engineering methods and standards that are applied throughout the project lifecycle to deliver appropriate cost-effective solutions.*"
    - ISPE Baseline Guide, Volume 5
- The application of well understood, easy to use GEP's *enables* the delivery of effective integrated C&Q projects.
- New Good Practice Guide from ISPE is approved on GEP outlining core concepts and core practices- available from www.ispe.org

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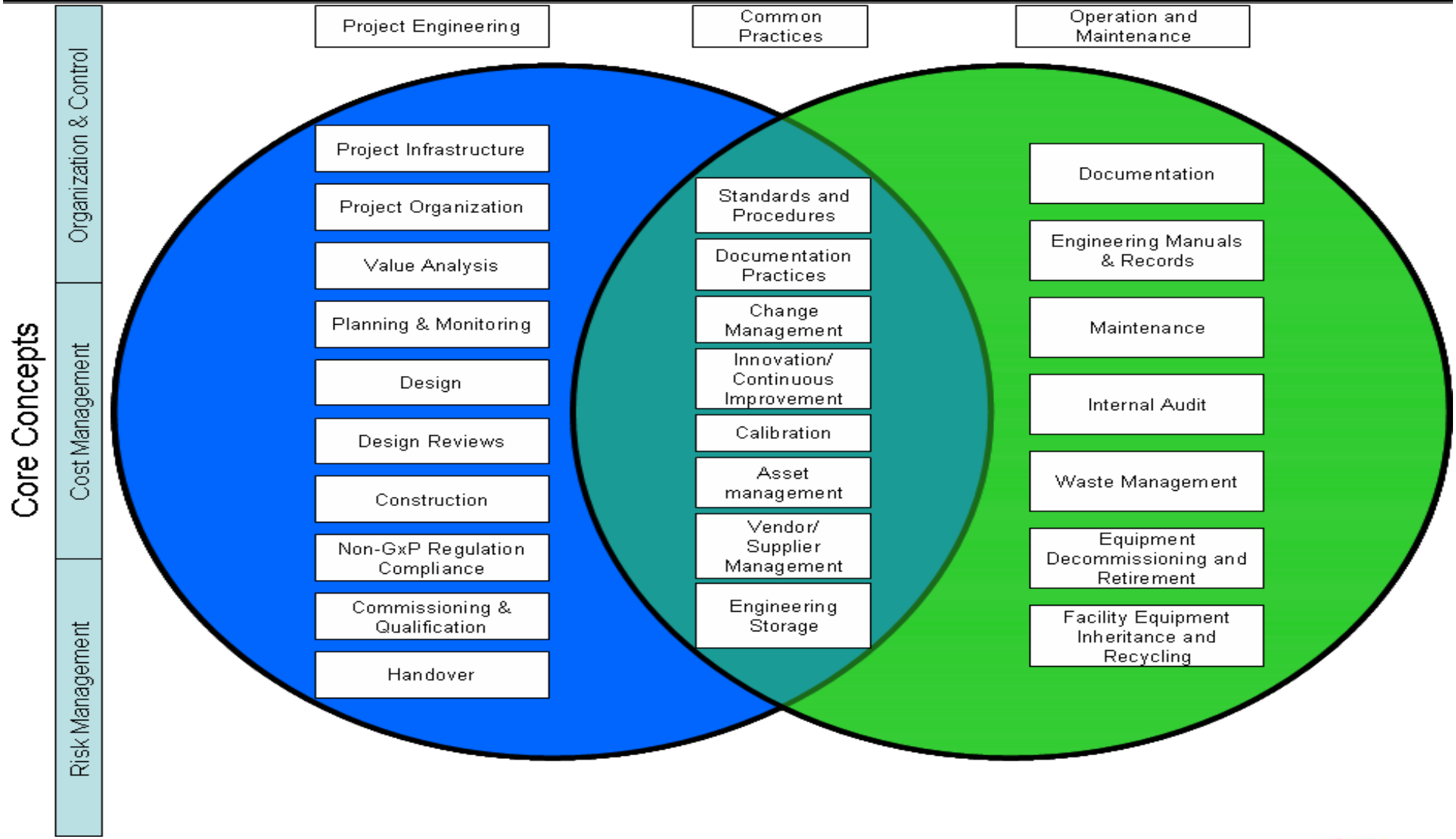
2. Best Practice Commissioning and Start-Up
Good Practice Guide – GEP, 2008 Key Concepts

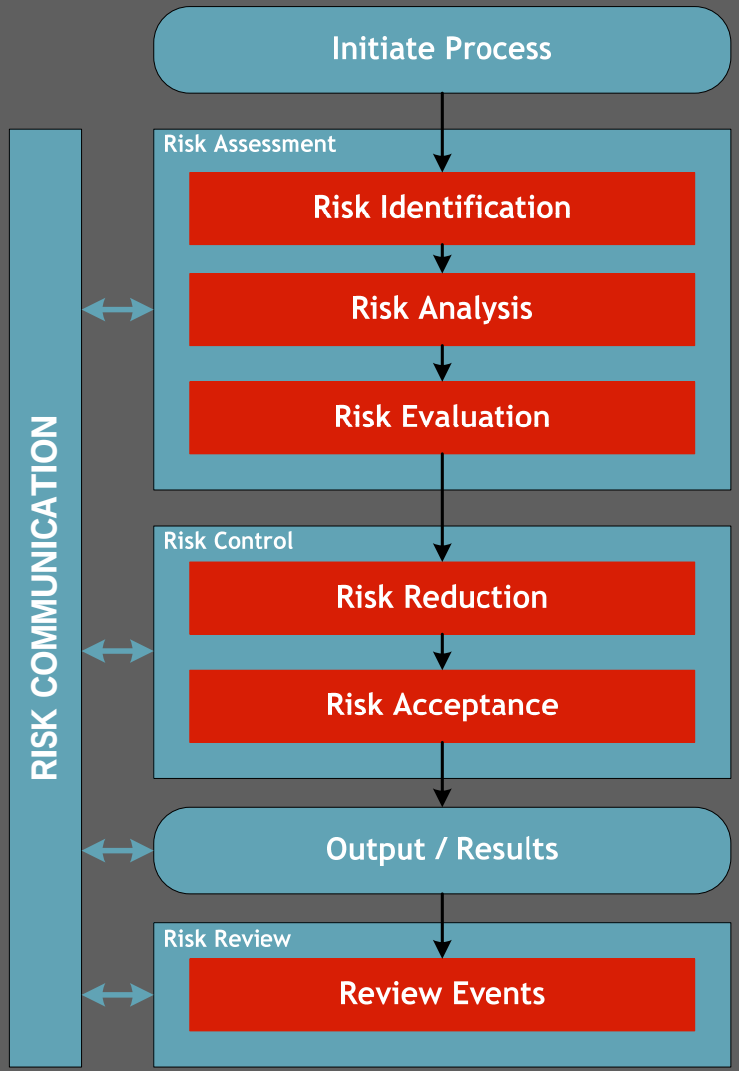


2. Best Practice Commissioning and Start-Up - Ongoing Focus on GEP's

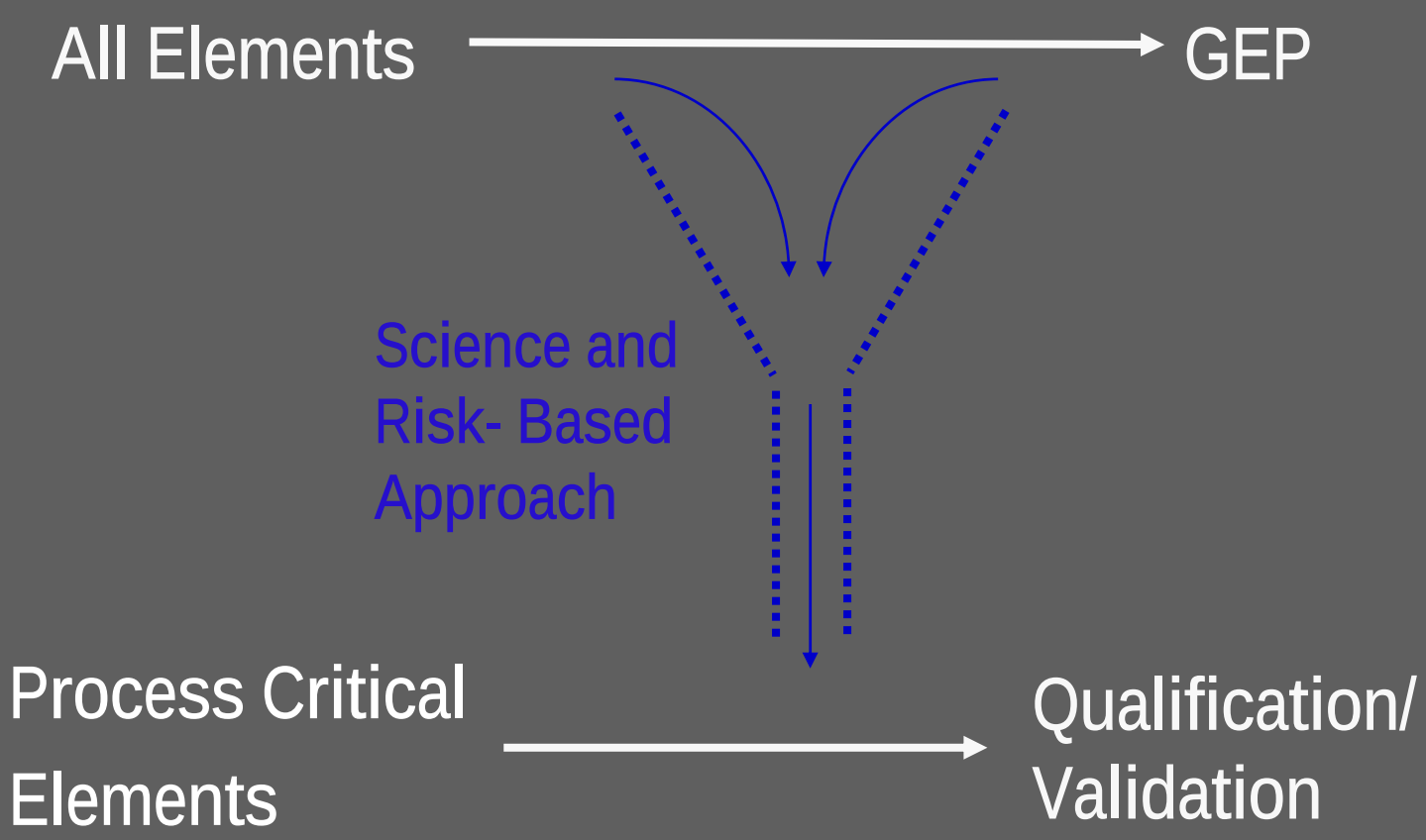
"The concept of a focused qualification effort is based on the assumption that these good engineering practices, and in particular a robust commissioning process, have been used to ensure the equipment, systems and associated automation and controls are acceptable from an engineering perspective and are fit for the purpose of meeting user requirements."

3. Risk Assessment to Focus Qualification on CPP's and QCA's

ICH Q9 Risk Assessment Mode



3. Risk Assessment to Reduce Qualification Load Reducing the Load – All design criteria



3. Risk Assessment to Reduce Qualification Load Some Tools Relevant to C&Q

Item	Note
System and Component Assessment	**Identify and qualify direct impact systems.** **Identify critical components to reduce qualification requirements.**
Family Approach/ Equivalence	**Group identical vessels to reduce OQ and PQ testing.**
Functional Risk Assessments	**Identify Critical Functions**
FMEA	**Failure Modes and Effects Analysis**
Process Risk Assessments	**Identifying Process Risks**
Functional Component Criticality Assessments	**Identify Critical Functions**
Quality Risk Assessments (QRA's)	**Based on the outcomes of the risk assessments the critical aspects for each direct impact system shall be identified.**

Many more tools available, but should always be based on science and knowledge, and performed by a subject matter expert with support from the complete multidiscipline team

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4. Leveraging and Utilising Vendor Testing to Maximum Impact

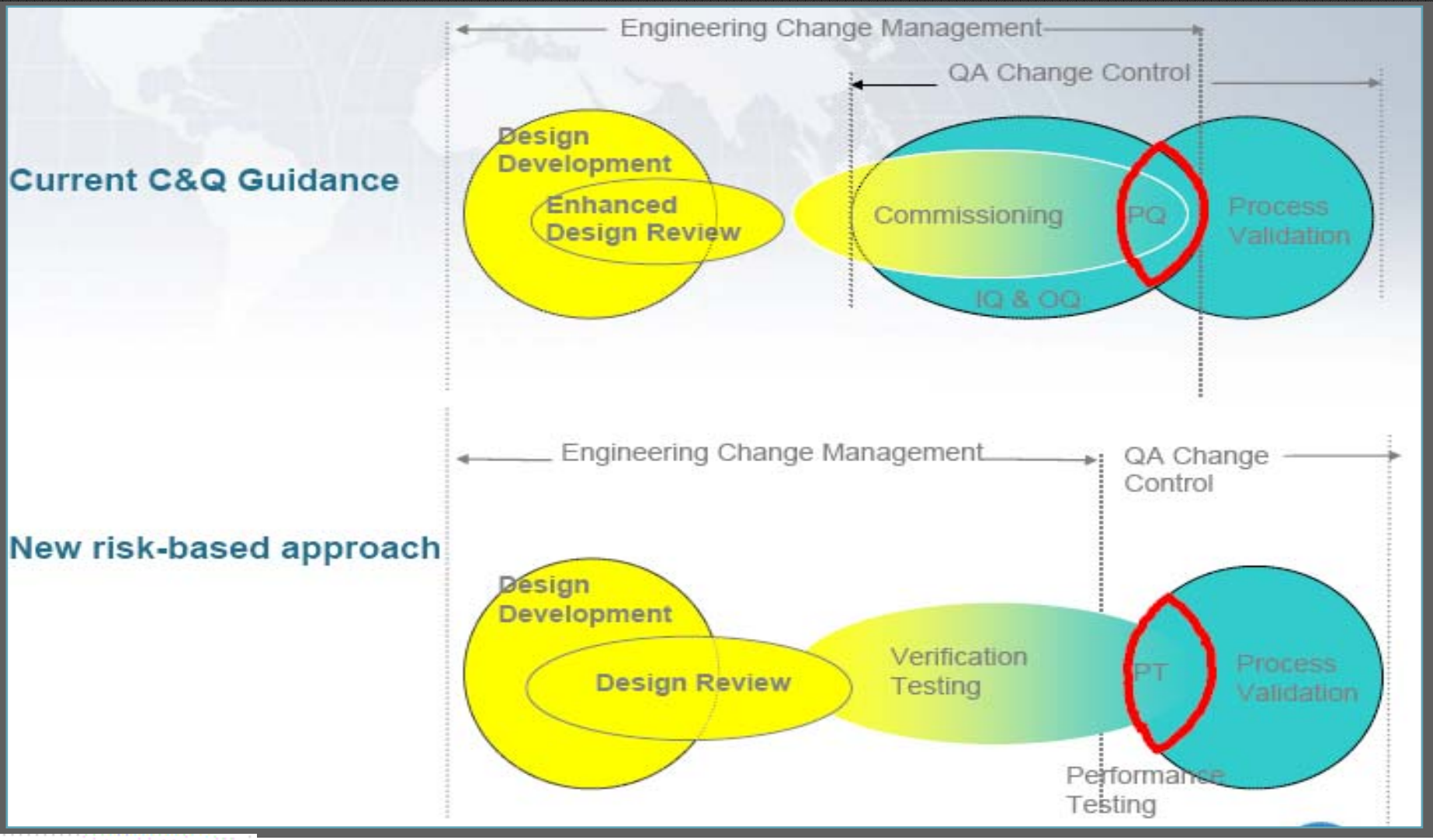
Leveraging

- Leveraging can be defined as the process by which testing or verification from one phase of the project is used to substitute or enhance testing or verification of another phase of the project. (Either Vendor Dossier/Construction to Commissioning or Commissioning to Qualification).
- Should be identified up front in the testing matrix
- For Information or tests to be leveraged :
  - The test must have been successfully completed, and pass its acceptance criteria,
  - Reviewed by a competent project team member,
  - Good Documentation Practice (GDP) must be adhered to,
  - Change control must be in effect.

4. Leveraging and Utilising Vendor Testing to Maximum Impact

- Vendor Testing
  - Can be a Major Leveraging source
  - This must be planned at the procurement phase and built into the commercial contract
  - Advantages
    - Vendor is an expert- so should be less cost
    - Makes handover clear “only when it works”
    - Encourages “turnkey” thinking
  - Some Pitfalls
    - Bad Document Quality/ practices
    - Poor Change Control
    - Less control by Customer
    - Training opportunity lost

5. Change control strategy across the project lifecycle.



5. Change control strategy across the project lifecycle.

- Change Control Notes
  - Robust Change control required at all stages of design and construction.
  - Keep it Simple…….
    - Competent Peer Review
    - Regular Review thorough audits
    - Detailed analysis of the impact of changes
  - Expectation should be that at handover from construction / Mechanical completion all drawings, dossiers and specifications are red lined and as-installed
  - Leveraging often confuses start of QA change control agree the ground rules at project initiation

References and Acknowledgments

- ISPE Baseline guide 5
- Draft ISPE baseline guide 12 ‘Verification’
- GEP best practise Guide
- ICH Q9
- Lean C&Q Webinar ISPE Mar 2009

Question and Answer Session