PharmOut

Validation – An International Perspective

Agenda

- Perceived industry problems - From QTPP/PQA → Process Validation
- Paradigm shifts
  - Process Validation based on QbD, Design Space, etc.
- Incremental changes
  - Plain vanilla validation – Annex 15
  - Integrated C&Q – ISPE Baseline
  - ASTM E2500

What are the perceived problems in our industry ?

- Variable quality of drugs/medicines.
- Poor Manufacturing practices.
- High costs.
- Too many batch failures & product recalls.
- Poor product specifications.
  - CQAs not fully understood.
  - Means CPPs not fully defined (risk not managed).
- Post-approval manufacturing changes resisted, leading to limited process improvement.
  - Slow process.
  - Too cumbersome.
  - Insufficient information from the pharmaceutical development of products.
- Not widespread use of PAT, QbD, Quality Risk Management, etc?

ICH is on the case !

- ICH Q8 ~ Guideline on Pharmaceutical Development
- ICH Q9 ~ Guideline on Risk Management
- ICH Q10 ~ Quality Management: Utilisation of science and risk-based systems to enable post-approval change & improvement"
- ICH Q11 ~ Development and manufacture of drug substances (chemical entities and biotechnological/biological entities) Recognises vital link API→ Dosage form.

Paradigm Shift – Process Validation

- Regulatory perspective
  - US FDA driven
  - EU following
  - Other nations variable
- Essential shift
  - Risk & Science based (ICH Q8,9,10)
  - Continuum to maintain the validated state
  - *In other words, a higher degree of control is appropriate for attributes or parameters that pose a higher risk.*
  - 3 Stage Process Validation (US FDA)
    - Process Design
    - Process (Performance) Qualification
    - Continued Process verification
  - No mention of 3 magic batches
  - No mention of Facility/Equipment Qualification

Incremental Shift- Qualification

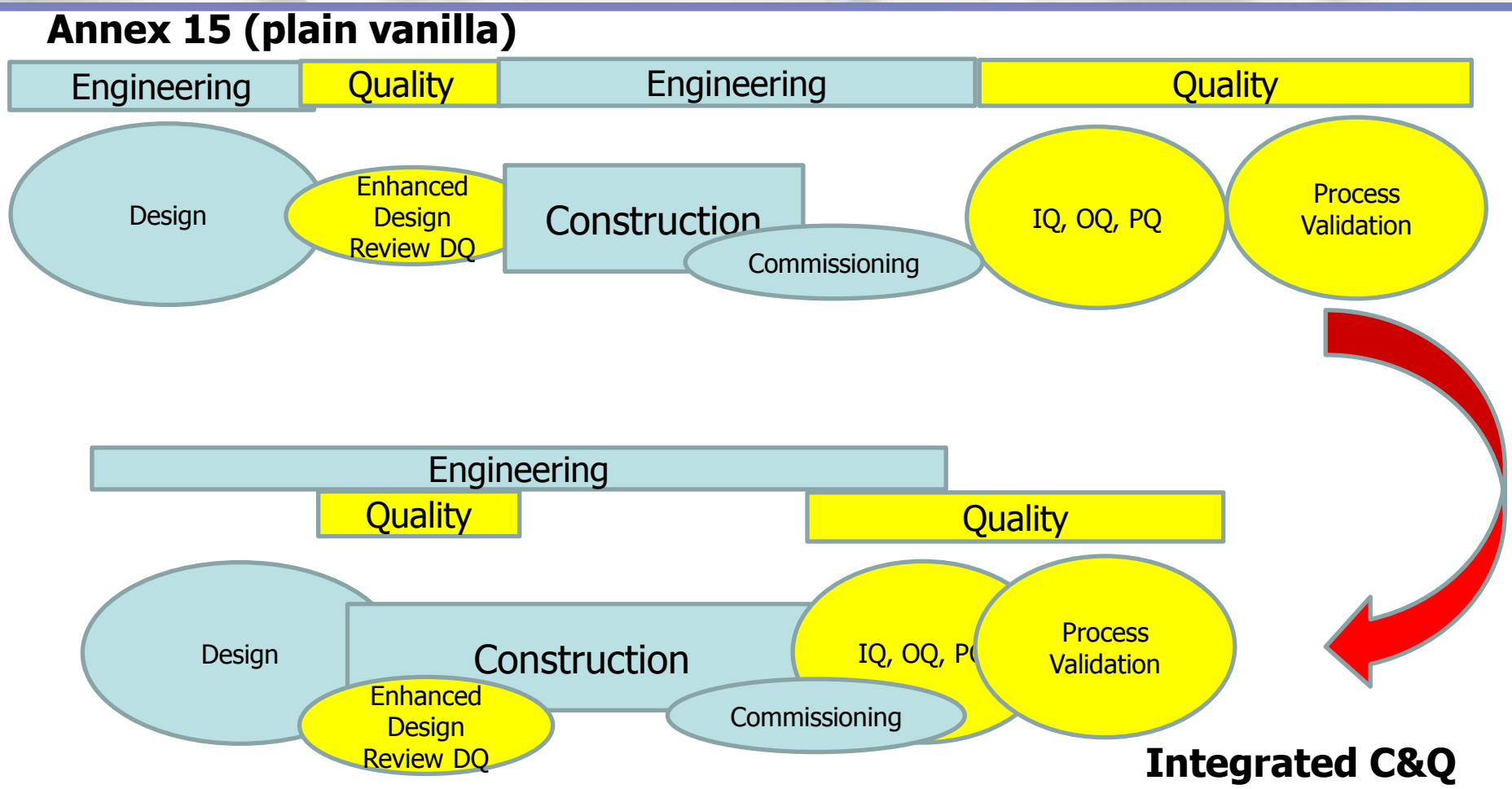
- Annex 15 [Plain vanilla validation]
  - Seems rigid DQ→IQ→OQ→PQ.
  - In EU, where created, it is guidance NOT a regulation or law.
  - Actually "Risk Based" approach is suggested *"A risk assessment approach should be used to determine the scope and extent of validation."*
- ISPE Baseline Guide (vol 5) Commissioning & Qualification [Integrated C&Q]
  - Leverages efficiency and focus by recommending.
  - Systems be identified by Impact on product quality.
  - Components be identified by criticality.
- ASTM E2500 [Brave new world for some]
  - "Standard for specification, design, and verification of pharmaceutical and bio-pharmaceutical manufacturing systems and equipment.
  - Reliance on verification of suitability by subject matter experts.

PharmOut

ASTM E 2500-07 What is it?

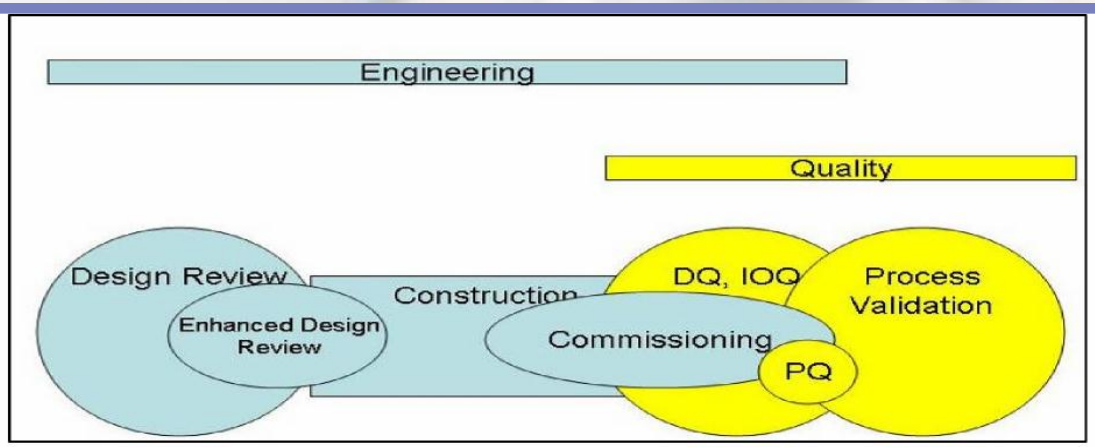
- US & US FDA driven.
- "A risk-based and science-based approach to the specification, design, and verification of manufacturing systems and equipment that have the potential to affect product quality and patient safety."
- "The overall objective is to provide manufacturing capability to support defined and controlled processes that can consistently produce product meeting defined quality requirements."
- Approved June 1, 2007. A voluntary consensus standard.
- Stresses expert analysis of critical elements that affect product quality.
  - Quality, (not Quality Assurance or Quality Unit) appears 44 times
  - Expert appears 21 times
  - Critical appears 20 times

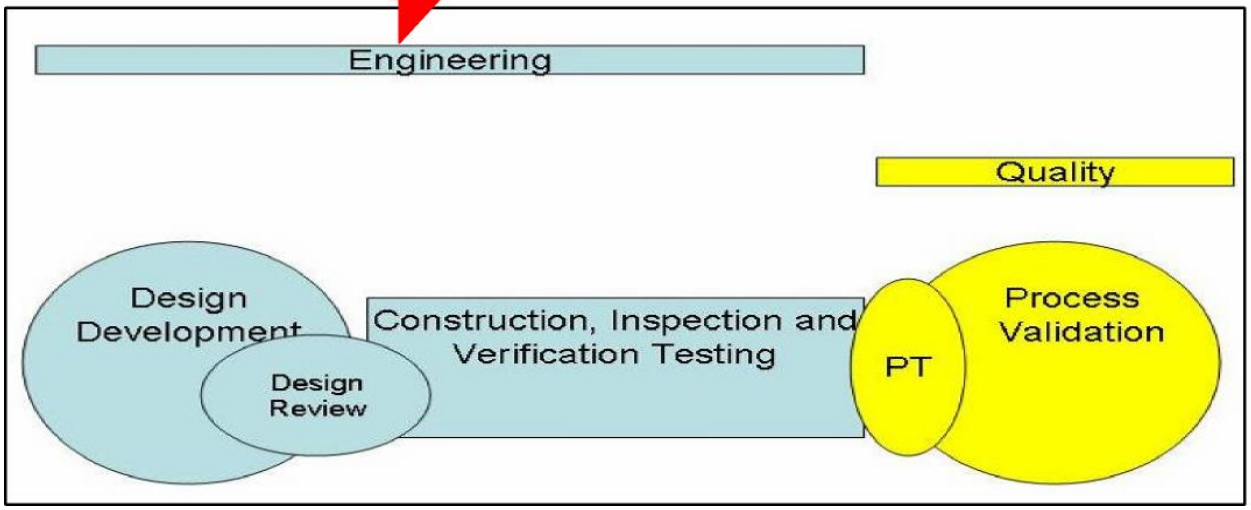
ISPE Baseline vol5 is about this!



ASTM E2500 is about this!

Integrated C&Q





ASTM 2500

PharmOut

My experience in the real world

- In emerging nations:
  - Plain Vanilla → Integrated C&Q
    - Pharmaceutical firm's QA reluctant to relinquish responsibility (power & influence).
    - Regulatory authorities inexperienced to adjudicate "Risk Based" practices.
    - No confidence in vendors & contractors.
  - Brave new world (ASTM E2500)
    - Not on the radar. US oriented.
    - A step way too far.
    - Reluctance/inappropriate to pass things to vendors.
    - Unlikely to find SMEs.
  - Process validation change not contemplated

My experience in the real world

- In developed nations:
  - Plain Vanilla → Integrated C&Q
    - Well accepted.
    - Some vendors and contractors fail to deliver.
  - Integrated C&Q → ASTM E2500 (Brave new world)
    - Embraced by a few.
    - Still some QA concerns about loosing control.
    - Not Annex 15 compliant (if considered a regulation).
  - Process validation embraced by a few, mainly big pharma.

Summary of the incremental shift in validation qualification

- Avoid duplication of inspections and tests.
- Computer and control/automation system validation integrated with other disciplines (GAMP still the favoured toolbox).
- Pass more responsibility to capable vendors and contractors.
- Make DQ work harder
  - More structured and thorough process.
  - SME does verification.
  - Confirm URS is complied with.
- IQ becomes an engineering technical function.
  - Integrated with general engineering QC.
  - Systematic checking for completeness.
  - QA oversight.
- More effective Performance Testing
  - Integration testing of whole system.
  - Challenge testing.
  - Proves fitness for purpose.

Reminder - Objectives of qualification

- All validation steps should confirm good news, not find problems.
- All the real work is done in the project discussions. If we start basic discussions during validation ….IT IS TOO LATE!
- Provides platform for QA oversight on systems that have a direct effect on product quality.
- Annex 15 of the EU/PIC-S GMP addresses validation in a more rigid way.
- ASTM E2500……Helps manage the work burden by using experts and risk based thinking to concentrate the qualification effort.

Thanks for your attention

PharmOut