Effective Implementation of Risk & Science Based C&Q Methodologies

An Operational Excellence Approach to Validation of Pharmaceutical and Biopharmaceutical Facilities

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08–NOV-2013

Connecting a World of Pharmaceutilcal Knowledge

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Background

- It is a global market
- The world is getting smaller and our jobs span more miles!
- It seems to be more complex - a multitude of regulatory bodies – more Regulatory pressure
- Projects have to be delivered faster to meet “speed to market” requirements once capital is released
- Aging facilities that have to comply with current and now, varied standards and expectations

Background

- C&Q direct costs (expensive) and indirect costs (delays to market or loss of capacity) are a big concern
- We need strategies that will focus on value and remove waste
- Compliance must be attained at the best cost possible.

Objectives

- Learn about a number of current and new Industry tools for planning effective and efficient C&Q projects.
- Learn about conceptual and actual approaches to keep focus on adding value and minimizing waste.
- Understand how planning pays off.
- How to take ownership on C&Q.

HOWEVER…We are all concerned and fearful about…

What kind of Pickle can we get ourselves into with the Regulators?

Agenda

- Industry and Regulatory Perspective - Direction
- Distilling the Ocean - the key concepts
- Current Practices in Use
- Concepts of Risk and Science applied to Verification (C&Q)
- Leveraging Knowledge and Expertise
- Document Management
- Reduction of Life Cycle Costs using these approaches

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INDUSTRY AND REGULATORY PERSPECTIVE

Regulatory Basis -FDA

In the Final Report *Pharmaceutical CGMPs For The 21st Century - A Risk-Based Approach* FDA described how their objectives included the following:

- **Encourage the adoption of concepts of risk management quality systems approaches by the pharmaceutical industry**
- **Encourage industry to use good science and new technological advances for all aspects of pharmaceutical production and quality assurance**
- **Encourage innovation leading to improved benefit to the patient**
- **Focus both industry and Agency attention on critical areas**

Annex 15 – Qualification & Validation

- Significant changes to the 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 the scope and extent of validation.**
- Design Qualification - The compliance of the design with GMP should be demonstrated and documented.
- Includes traditional VMP/IQ/OQ/PQ terminology.

Relationship of ASTM Standard to GMP Regulations and Guidance Documents

US GMPs

EU GMPs

Japan GMPs

Basis of our Program

Equipment…shall be of appropriate design, adequate size and suitably located….for its intended use…cleaning and maintenance (21CFR11.63)

ICH 08, 09, & 10 Guidance (ASTM E2500)

The level of effort, formality and documentation of the quality risk management process should be commensurate with the level of risk. ICH Q9

ISPE Baseline® Guides

How to perform key elements of Science and Risk-based approach and determine 'Suitability for Intended Use'.


Guidance for Indu

Q8 Pharmaceutica Development

INTERNATIONAL CONFERENCE ON HAI REQUIREMENTS FOR REGISTRATION OF P USE

ICH HARMONISED TRIPART

QUALITY RISK MAN Q9

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

PHARMACEUTICAL QUALITY SYSTEM Q10

Guiding Principles for *GAMP® 5*
Quality Risk Management Strategy

- **Make use of a reasonable risk-based approach**
- **Risk should be tied to *potential impact on patient health***
- **Focused "Top-down" approach**
  - **Look at *processes* before *systems* or *functions***
- **Forward-looking**
  - **Compatible with evolving initiatives like ASTM, ISPE Guides, PQLI**
- **Emphasize assessment and management of risk**
- Consideration and compliance with regulations

"We recommend that you base your approach on a justified and documented risk assessment and a determination of the potential of the system to affect product quality and safety, and record integrity."

— *FDA Guidance for Industry: Part 11, Electronic Records; Electronic Signatures — Scope and Application (2003)*

Risk-Based Approaches / ASTM

- **ASTM E2500-07**;
- Two new ISPE guides:
  - Applied Risk Management for C&Q
  - **Science and Risk Based Approach - Delivery of Facilities, Systems, and Equipment**
- FDA / EU Acceptance of Risk-Based Approaches
- Company/Industry Perspective
  - Traditional IOPQ = *Few*
  - Some form of Risk Assessment + Leveraging of GEP = *Majority*
  - Pure ASTM = *Several but eagerly growing*

Risk Based Implementations

- Amgen Corporate Verification Methodology
  - Utilizes basis of ASTM E2500-07 for Verification
  - Sterile Manufacturing Site (Puerto Rico) and Clinical Site (Thousand Oaks, CA) for Aseptic and Sterile production using this process
- Auxilium Biotechnology
  - Licensed facility that used full ASTM in US for EU and US products
- Shire HGT – Lexington, MA
  - Utilized hybrid of ISPE Baseline Guides and ASTM E2500-07 for currently licensed facility (EU and FDA) for Biotech product
- Pfizer Corporate has fully developed and is implementing full ASTM E2500-07 based methodology
- Abbott Laboratories
  - Implementing on projects

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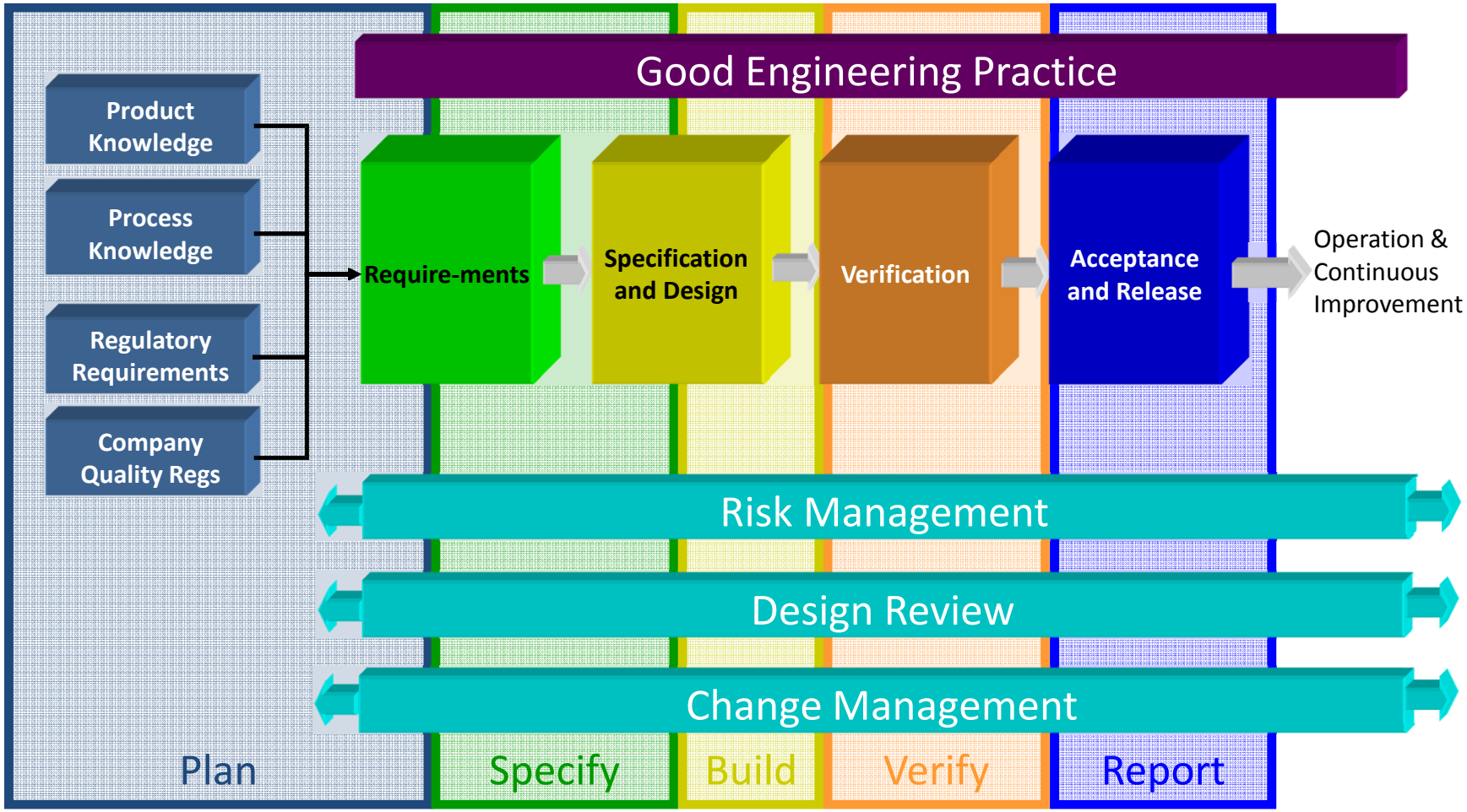
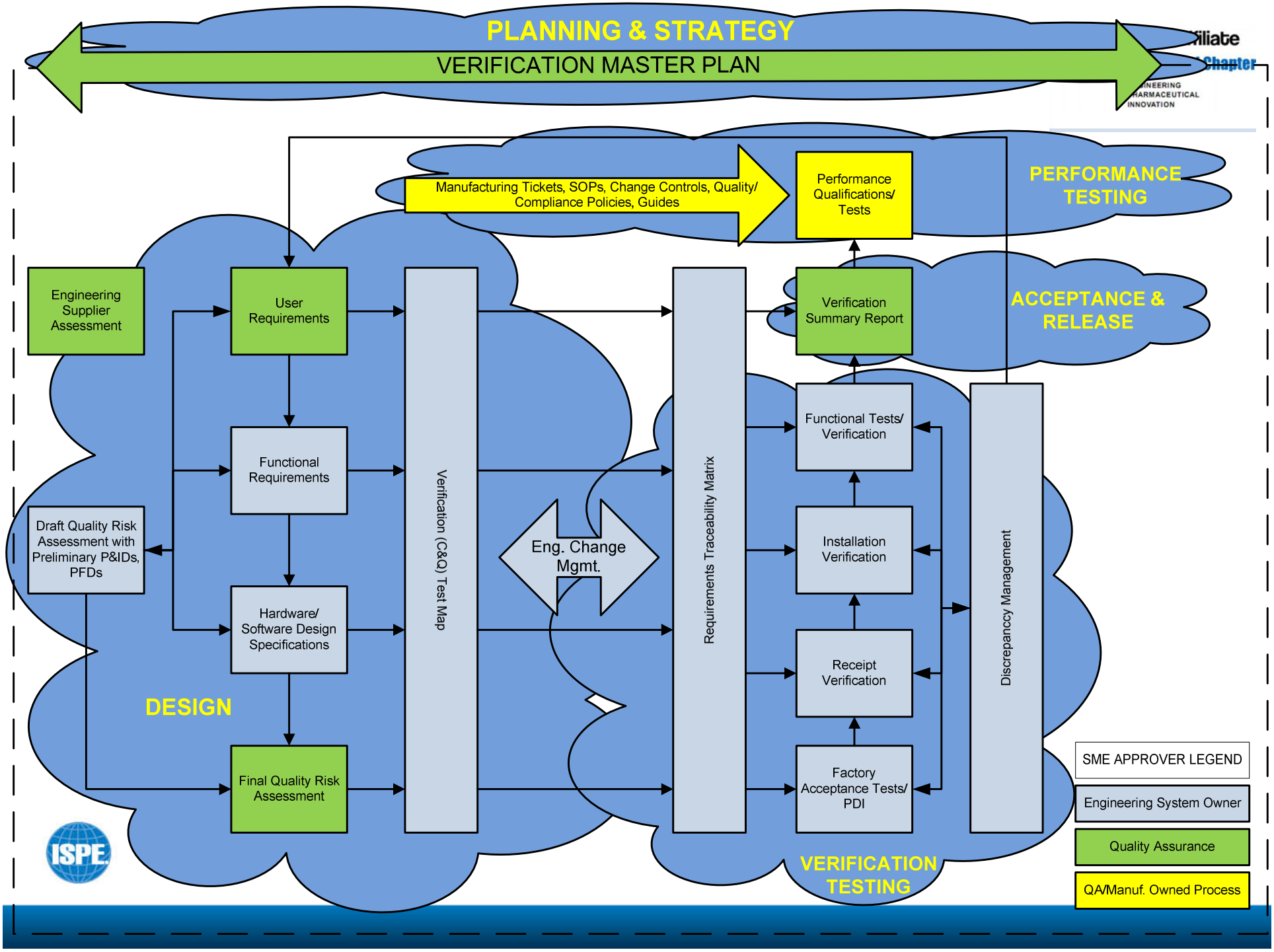
ASTM E2500-07, ISPE Guides

GAMP® 5 & ASTM E2500 Processes Overlaid




PLANNING & STRATEGY
VERIFICATION MASTER PLAN
Manufacturing Tickets, SOPs, Change Controls, Quality/ Compliance Policies, Guides
Performance Qualifications/ Tests
PERFORMANCE TESTING
Engineering Supplier Assessment
User Requirements
Verification Summary Report
ACCEPTANCE & RELEASE
Functional Requirements
Functional Tests/ Verification
Draft Quality Risk Assessment with Preliminary P&IDs, PFDs
Verification (C&Q) Test Map
Eng. Change Mgmt.
Requirements Traceability Matrix
Installation Verification
Hardware/ Software Design Specifications
Discrepancy Management
Receipt Verification
DESIGN
Final Quality Risk Assessment
Factory Acceptance Tests/ PDI
VERIFICATION TESTING
SME APPROVER LEGEND
Engineering System Owner
Quality Assurance
QA/Manuf. Owned Process
ISPE

Why?

Rationale & Benefits

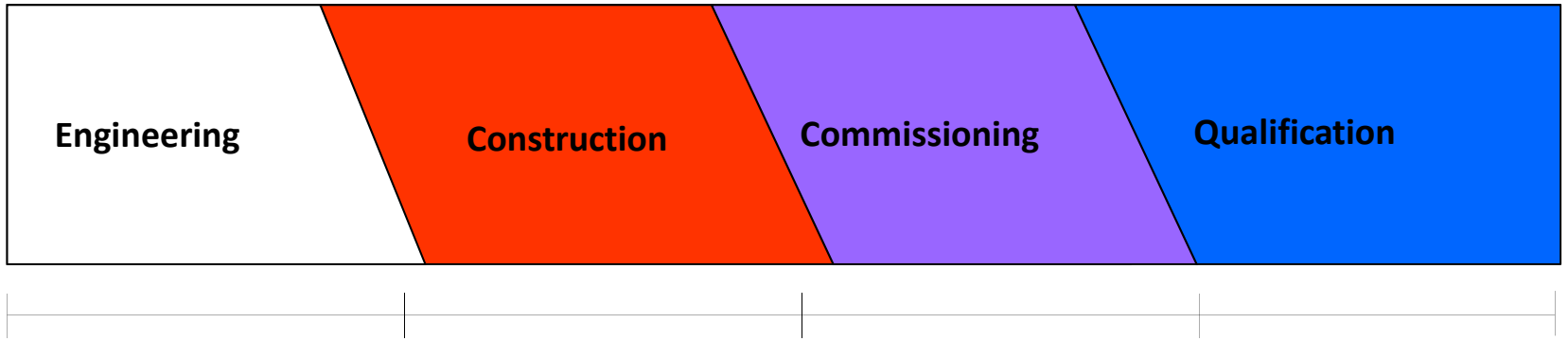
- Focuses design to identify the critical elements that affect product quality early on that then…..
- Focuses qualification/verification activities on "critical" elements and areas of highest risk
  - Less Regulatory scrutiny on non-impactful design issues
  - More focus on what is important
  - Significantly reduce deviations during qualification
  - Results in cost savings and quicker utilization of assets

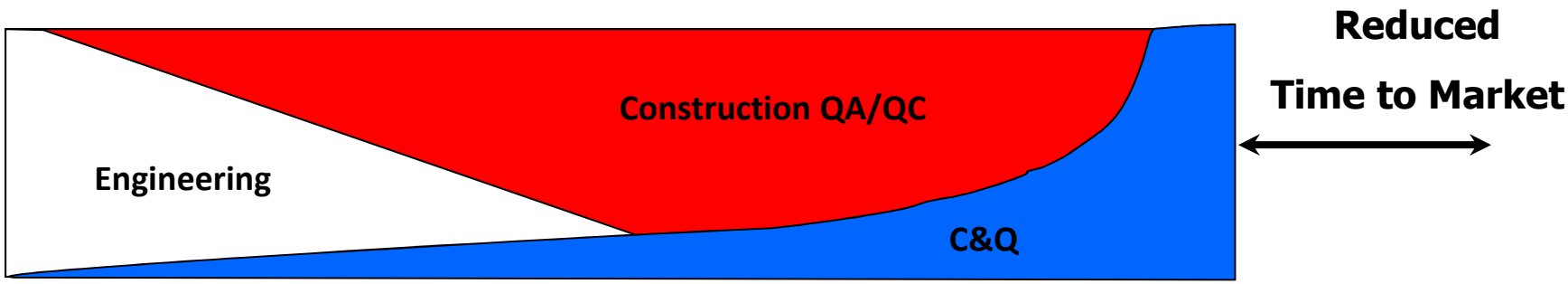
Rationale & Benefits

- Used to develop Risk-Based Calibration and Preventive Maintenance Programs
  - Reduced number of “critical systems”
  - This is biggest impact in the long run, lower COGs
- Allows Change Management to be tiered to levels of risk
- Greater Flexibility during project while maintaining control of critical issues
- Overall Reduced Cost with Increased Compliance
  - Less systems having to go through Regulatory Change Control, only through Engineering Change Management

Traditional vs. Integrated Approach (ICQ)

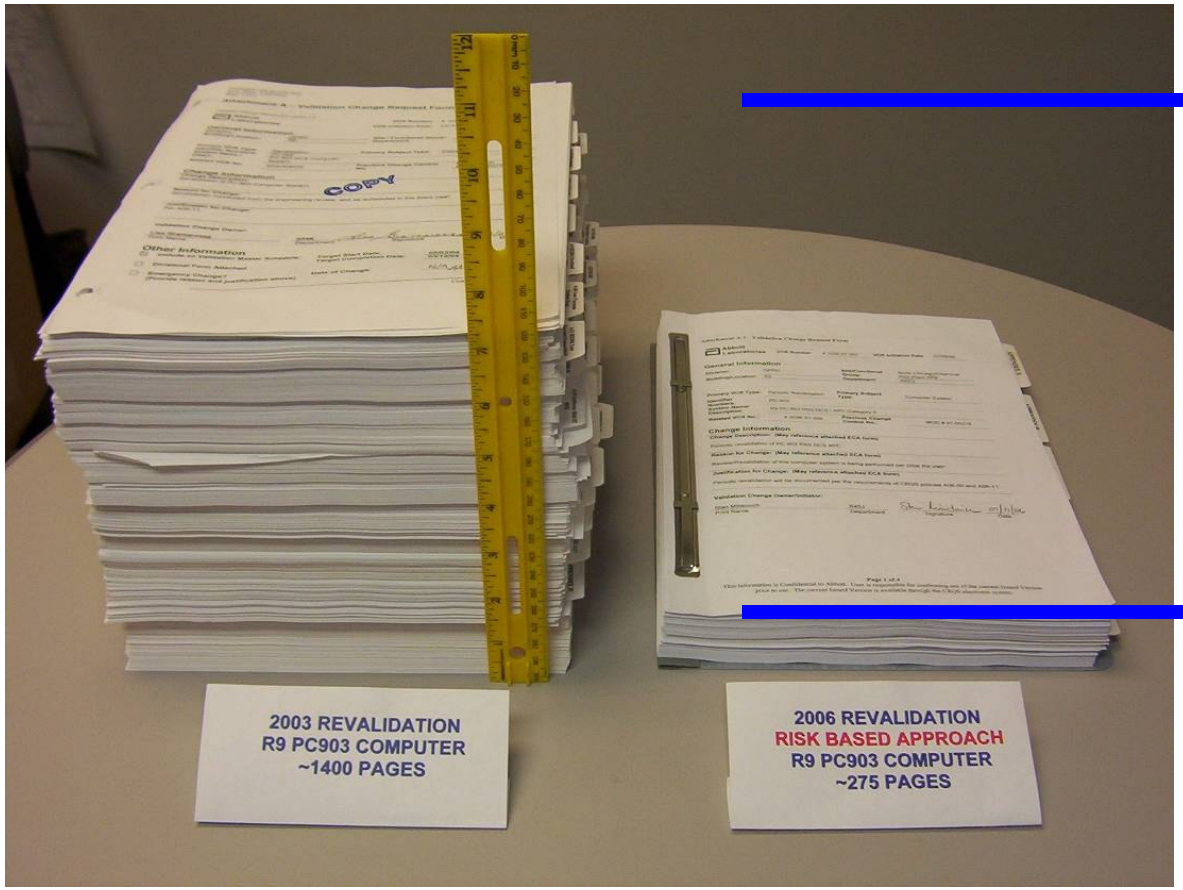
Traditional Approach





Integrated Approach

Eyes on the Prize



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Time & $$$
to
Focus on Critical Quality Issues

Actual photo of risk based revalidation paperwork for a legacy control system (on right) vs. previous revalidation “testing everything”

Application Principles

Basic Principles to Employ for more Effective C&Q Planning and Projects

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1. Treat the C&Q part of the project as all other parts of the project
   - Understand the process sequences and dependencies – integrate schedule and create true critical path
   - Understand the value of data being collected and why (who is the customer)
   - Collect the data at the time of greatest value and minimal effort
   - Understand critical path items
   - Develop a resource plan – logistics planning
   - Have clear roles and responsibilities
   - Control the documentation, not the other way around
   - Establish project metrics

Basic Principles to Employ for more Effective C&Q Planning and Projects

2. Identify your Subject Matter Experts and use them across department boundaries
3. Use Risk Management to guide your actions and improve compliant design and compliance outcomes
4. Use value proposition to guide your actions – remove waste – THIS IS KEY
5. Have a plan and work the plan
6. Use communication and tracking tools
7. There is not substitute for Good Engineering Practice
   - Includes good engineering change management

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Benefits to Supporting Quality Systems

Calibration

- Calibration requirements defined/based on process risk and criticality
- Set calibration frequencies based on risk
  - Process critical (≤ 1 year)
  - Process reference / troubleshooting (≥ 1 year)
  - Maintenance and troubleshooting (≥ 2 year or when suspect)
  - Non-critical (when suspect)
- Facilitates timely entry into calibration program
- Use of project information management system or ETOPs are the basis for equipment/instrument history files

Preventive Maintenance

- Preventive Maintenance defined on process and business risks
- Opportunities for “Operational Excellence” and support for operational/time based maintenance vs. schedule only based maintenance
- Implementation of status monitoring to mitigate areas of high risk

Change Management

- Develop tiered Change Management program based on risk model and assessment results
- Eliminates change control review, documentation, and approvals for non-critical (no impact on PQAs) activities
- Increases flexibility for maintenance of non-critical components
- Increased consistency in decision processes based on risk determination

Questions

Case #1

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Implementation of enhanced commissioning program at Large OSD and biologics site

- A bottom up approach
- Done over two small pilot projects – called “Enhanced Commissioning” approach
- Team was empowered to do things differently
- When asked by facilitator as to why they did things a certain way, they were not allowed to say “because that is the way that we do things”
- Mapped overall process and kept copy on project room wall
- Applied concepts of “customer” and “value” to data and procedures

Case #1

- Client was developing URS and other design documents after IFC was given!
  - "Who was customer and what was value?"
- Client wanted to map the lab for temperature
  - "Who was customer and what was value?"
- Applied impact assessments in a more focused approach
- Previous projects – all items were "critical" or Direct Impact"
- Ahh-Haa Moment – the difference between "important" and "critical"
- Who owns the "process"? – the PM or the Project Engineer
- Whose job changed the most? – The project engineer's did
- Quality person was best person for SME on sanitary tubing welding inspections, but never thought they could do it.

Case #1

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- Lessons learned
  - Job roles and accountability where key issues that created some of the situations they were in and caused issues on the projects – need to be flexible
  - The project showed that the implementation of these concepts was across the team with more focus on engineering job roles
  - Having empowerment to do and say things differently was very positive

Case #2

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Implementation of a Streamlined Engineering and Validation Approach – Major BioPharma

- A top down approach
- Develop Quality System documents that align and provide a basis for a “Lean Approach” to doing Engineering and Validation projects
- Aligned all documents into an ISO based hierarchy
- Looked at document Objectives and Scope
- Mapped current state and future state in terms of documents
- Policy, Guides, SOPs, WIs, forms
- Used value stream mapping approaches
- Used Lean Principles
- Concurrent implementation of Impact assessment model was being done and going well

Case #2

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- Key issues learned and uncovered:
  - A lot of “muda” in the current system
  - Guides were actually standards and deviation was not allowed from them
  - Someone would rather follow a procedure and do something they knew was very inefficient or wasteful versus change the procedure
  - Projects are not times to implement a full quality system change like this – the project takes precedent to all items when time and money are concerned
  - Needed a higher level sponsor
  - Engineering change management system was inadequate
  - Risk Management processes were not in place at a high level

Case #3

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Implementation of a Streamlined Engineering and Validation Approach at a major biologics manufacturer – Impact Assessments

- Implemented in two phases
- Retrospective approach (take current design and do impact assessment) – this was done on a +$40M renovation project. Went very well as the company validation director trained all groups in implementation of the program. Use outside facilitator (IPS) in key meetings
- Proactive approach (perform preliminary boundary and system impact analysis) and then follow up and update impact assessments during design reviews. This was done on a larger second project $200M+ green field site

Case #3

- Lessons learned
  - Pick one approach concept for a project and then stick to it, train in it and update and feedback on progress
  - Document planning and management proved to be very valuable and got many previous issues addressed early on in the project
  - Using planning tools like test matrices were very helpful
  - Being flexible – commissioning testing that failed might have to be tested in OQ due to time constraints not allowing for retest in commissioning phase. System needs to be aligned with these possibilities (the guides developed allow for this, see Top Down approach project)
  - On the initial projects, overall validation effort seemed same but time was gained on schedule do to better document management and paperwork flow.

Case #3

- Lessons learned, Con't
  - Early involvement by the respective SMEs in validation helped to create better P&IDs and GMP drawings earlier in the project.
  - Both facilities had PAIs with no comments on validation
  - There was strong pressure to go back to old ways and having a champion with penalties presented helped keep the team aligned
  - Lessons learned on the first iteration (Project) led to a better implementation on the second
- Client is promoting the success of this program with respect to meeting project timelines, cost management and project controls – presented at ISPE National and will be presenting at Interphex
- This last project was a FOYA honorable mention

Case #4

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Implementation of Impact Assessments for a Sterile Liquid and OSD pilot plant using isolation technology for containment and sterility

- One of first applications for Design reviews, System level impact, component level impact at major pharmaceutical manufacturer
- Commissioning was done by the CM.
- Lessons learned
  - The ability of the CM to adequately collect the supporting data and alignment with the qualification was determined early on before it could have impact. More guidance was then given and the C&Q firm developed the key commissioning documents that would be leveraged into the Qualification documents

Case #4

- Lessons learned Con't.
  - Document management was strong and saved time
  - Early Planning caught issues early before they had impact
  - Vendor commissioning and qualification was leveraged heavily and reduced the amount of 3rd party testing needed for the isolation line systems
  - Overall effort was about the same but project timelines were kept - more early on involvement allowed for saving time and hours on the end of the project.
- Facility got licensed
- FOYA award winner

Case #5

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Implementing a Quality Risk Assessment method at a major pharmaceutical manufacturer

- Implemented a QRA (Quality Risk Assessment) approach for a project
- Used FMEA model to show how to reduce testing currently done
- Lessons learned
  - Had no support in upper management nor had any visible support driven to the engineering team that had metrics that conflicted with implementation of the approach
  - The approach took the amount of tests done in validation (OQ) from 13 to 3
  - Owner is currently implementing these programs across projects (very slow)

Case #6

Using a Risk Assessment to determine room classification - Manufacturer of gel product applied to mucous membranes for prevention of viral disease

- Unusual manufacturing process
- Consultants informing them to have class 10,000 rooms for certain processing
- Applied a risk assessment model, Quality Risk Assessment with FMEA
- Justified Class 100,000 as most stringent requirement with better layouts and traffic controls once all risks were identified
- Facility passed authorized body inspection

Case #6

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- Lessons learned
  - General Manager participated and drove team to participate
  - All team member understood design basis and could explain to regulators GMP nature of design and key features that made it GMP
  - A relative short time and investment (two weeks total time, one consultant, not full time) saved close to two hundred thousand dollars in mechanical and construction costs.
  - Passed EU body inspection

Common Themes for Success

- Implementing the whole program at once does not work
  - "culture eats change"
  - Use a change agent, internal or external
- Develop a programmed approach with a vision
- Work in small portions, achieve success, gain buy-in
- Senior management buy in *and* participation is key
- Empower team to do things differently
- This is not just a validation based application, it is a whole business application
- Keep metrics for application of continuous improvements
- Use Lean concepts of Value, process and customer
- Job boundaries need to be flexible
- Roles and Accountability became a recurring theme

Common Outcomes/Observations

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- Engineering systems (GEP) and Engineering Change Management system are underlying programs that will need to be realigned for these programs
  - Affects engineering systems more
- Impact on Life Cycle costs relative to Maintenance and Calibration can be positive, but those systems need to be aligned to the system and component classifications
- Improved compliance through simplicity in systems and application of risk management
- Risk Management program in company needs to be implemented – companies are doing this in the Quality areas of responsibility
- Commissioning needs to focus on all value driven areas, not just on supporting validation to get the most out of commissioning