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Engineering Case Study:

Compliant, Productive and Automated Commissioning, Qualification and Verification (CQV) Process - Streamline and lean out your CQV process and use an eSolution to embed it across the organization for years to come.

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2 Executive Summary

This paper outlines the business process changes that achieve a simplified more streamlined risk-based Commissioning, Qualification and Verification (CQV) process and how the application of an electronic CQV technology will embed this lean methodology across your organization, enabling a structured repeatable process that increases productivity and enhances compliance for years to come.

It details the rewarding outcomes that one can expect based on successful industry deployments - a lean cross-site harmonized process delivering productivity, reduced cycle times, compliance and data integrity benefits.

The new automated process provides a compliant, productive, simplified ASTM E2500 methodology with early-on issue identification and real-time information/data access together with status tracking, schedule cycle-time assurance and project documentation change management.

3 Background

To ensure products made in the Life Science industry comply with regulatory requirements, established validation methodologies are used to test and document the systems and processes involved in product

manufacture and release. Engineering consulting firm Encova Inc. has provided Design, Commissioning and Validation Services to Life Sciences for more than 16 years and has long recognized the time, resources and finances their clients devote to validation and compliance. Despite great advancements in the validation profession, the validation of new systems and the process of maintaining the validation state remains complex and costly. Design issues identified during the later stages of a project commonly result in even greater costs and delays than when identified and eliminated early. These challenges are further exacerbated by the need to assure compliance, improve time to market, increase facility utilization and improve productivity.

3.1 Promising areas for improvement include:

1. Adoption of a risk-based approach based on ASTM E2500
2. Application of an electronic CQV (eCQV) technology which includes electronic records creation, execution and management capabilities

Regulatory agencies promote a risk-based approach and electronic systems with benefits of assuring data integrity compliance, reducing and simplifying the quantity and complexity of documentation to review as well as improving the use and management of supporting data for continuous monitoring.

3.2 Old versus new process

Regulatory requirements for validation have been in place for many years. The traditional paper-based and manual efforts approach may still be compliant and provide the desired outcomes. However, it does not provide the desired improved process and engineering efficacy benefits of the proposed approach.

At the high-level validation types may be separated into two categories – process validation and equipment validation

Process Validation	Equipment Validation
Manufacturing Process	Equipment
Cleaning	Computer Systems
Methods	Laboratory Instruments
Sterilization Process	Facilities
Utilities Process	Utilities
Shipping Process	Automation
Sanitization Process	
Packaging	

3.3 Common Validation Activities, Deliverables and Challenges:

Subject matter expert (SME) skills are necessary for each validation type. However, in general all validation types have common tasks and require similar, if not the same, deliverables as outputs to these activities. Likewise, the challenges are similar across all the validation types.

Common Validation Activities	Common Validation Deliverables
Validation Planning	Validation Questionnaire/ Master Plan
Requirements Management	User Requirements and Trace Matrices
System Design	Functional Specification
Risk Assessment	Risk Questionnaire/Protocol
Design Review	Design Data/Design Review Documents
Test Script Prep	Val Protocols & Tests (Pre & Post Approved)
Trace Matrix Create	Trace Matrix (URS-Design Elements-Test-RA)
Testing	Executed Testing Records, Deviations
Deviation Processing	Close out, Retest and Supporting Documentation
Val close out	Val Summary Report, Post Approval
Training	Procedures
Val Records Storage	Controlled document management
Maintain Validated State	Periodic Review Assessment, requalify if required.

3.4 Typical Validation Process Challenges:

Records Management and real-time status of all project activities and deliverables
Inefficient, resource intensive, long cycle times, susceptible to error
Coordination and GXP Capture of validation data from many sources (vendor, engineering etc.)
Validation records review and approval cycles (design, protocol, test, trace, final summary)
Test Execution and Final Summary Reporting (typically paper-based and manual efforts)
Data Integrity Compliance (i.e. ALCOA Principles)
Record Storage, Search and Retrieval of Val Information
Data Integrity Compliance (i.e. ALCOA Principles)
Leverage Common Information and Best Practices across Projects & Sites

3.5 Business Pain Points

Focusing on the Validation process for new equipment and systems provides the opportunity to analyze the emerging risk-based approach, often referred to as CQV and how an electronic solution can embed this methodology. The improvements outlined in this paper can also be applied to all other types of validation.

3.6 What makes CQV a different type of Validation:

Scope	<ul style="list-style-type: none"> Commissioning addresses both GxP and non-GxP requirements (Health & Safety) Scope: Single piece of equipment or a new facility with much equipment and new utilities The design, assessment and qualification phases can include Factory Acceptance Testing (FAT), Site Acceptance Testing (SAT) and Performance Qualification (PQ)
Complexity	<ul style="list-style-type: none"> Many components and multi-sourced data to manage - equipment, facilities, utilities Managing the list of items and deliverables with ongoing project changes-additions, modifications and deletions. The process needs both control and flexibility
Commonality	<ul style="list-style-type: none"> Items have common purpose, design, functionality, testing requirements Items may be the same as items previously validated/qualified
Responsibility Sharing	<ul style="list-style-type: none"> Overall project size and complexity requires support of many different resources - vendors, engineering and construction services, company staff CQV validation data and testing responsibility includes equipment vendors, service providers (construction, engineering) and company staff (final verification - PQ and overall review & approval. Responsibility assignments must be effectively managed

4 Traditional C&Q Process:

- Phases: Engineering-> Construction-> Commissioning-> Qualification-> Validation
- Each phase of the project is treated as a defined step. Phases and individuals working on each phase tend to be siloed and information is not shared effectively
- Information is passed to next step through documentation (not through effective knowledge transfer)
- At each phase, individuals must mine data from the previous step
- From design to construction to commissioning the quantity of system or equipment information increases and becomes more detailed, isolated and challenging to remediate design/build issues.
- Each phase of the process utilizes separate Subject Matter Expert Review & Control (Silos)

4.1 Issues with Traditional C&Q Process

Timing	<ul style="list-style-type: none"> When activities are done (i.e. design not completed /approved, commissioning not completed, testing protocols prepared too early - validation testing starts prior too early-may need to redo/take risks) Level of change management (when to apply controls - changes not effectively tracked/controlled at early phases) Understanding & leveraging work from previous phases to avoid redundant work Identifying/correcting design & construction issues at earliest process phase
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Amount & Benefits of Testing	<ul style="list-style-type: none"> • Redundant testing at all phases - issues identified late in process add more cost & time to correct • Level of testing high at later phases - testing not phase based /risk based, not based on critical quality aspects (CPP/CQAs)
Documentation	<ul style="list-style-type: none"> • Storage/control (paper & electronic records, not in one place, where to store etc.) • Movement and access of records for review & approval. Logistics: where are documents. • Data Integrity – difficult to maintain data integrity (DI) with paper-based records (ALCOA)
Data Management	<ul style="list-style-type: none"> • Technology transfer of records • Data source management • Data mining/sharing information

5 Validation Process Improvements Identified by Industry:

Validation/C&Q methodologies have advanced over the last 10 years to include concepts such as ASTM E2500 and Risk Based Verification. FDA and other regulatory agencies have endorsed innovative validation processes that provide the required level of assurance but are also efficient, effective and compliant.

Traditional C&Q	<ul style="list-style-type: none"> • Commissioning followed by validation - FAT, SAT, IQ, OQ, PQ • All requirements tested in all phases • V-model
ASTM E2500	<ul style="list-style-type: none"> • Risk & science-based approach to C&Q • Aligned with concepts of ICH Q8 and Q9 • Quality unit responsibilities targeted on high-risk requirements • Introduces new concept of verification
Risk based verification	<ul style="list-style-type: none"> • New terminology and process endorsed by FDA, ISPE based on good science, good engineering practices, good documentation and product and process understanding • Verify equipment suitability and all requirements during FAT based on design specs, risk assigned testing • Verify only high risk critical to quality requirements during SAT • Annex 15 aligned with ICH Q8, Q9, Q10, Q11 - CQV should be risk-based; can leverage testing based on risk assessment and science • Aligned with 3 stage PV guidance (Design, Functional Confirmation, Continuous Operational Confirmation/ Change Control)
FDA 21 st Century	<ul style="list-style-type: none"> • Innovative validation processes endorsed by FDA and other agencies provide required levels of assurance and are also efficient, effective and compliant.

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|--|
| <ul style="list-style-type: none"> • 2011 FDA process validation 3 phase guidance |
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The risk and phase-based approach decreases the amount of testing performed later during qualification, but increases the control needed on testing performed early in the process. Many commissioning programs do not incorporate controls or have a manual process for the controls (Engineering Change Management, GDP and Data Integrity) needed to satisfy the formal GMP qualification requirements. Use of an eCQV solution establishes controls without adding to the work load or decreasing flexibility. An eCQV solution increases the transparency and management of activities throughout the process.

5.1 New ASTM E2500 Methodology:

5.1.1 Concept:

Use phase appropriate testing to leverage information & data use across phases (design, engineering, construction, test, implement)

- Takes advantage of testing performed early in the process to reduce the amount, impact and cost of re-work and testing needed as the project progresses
- Reduces redundant testing across phases
- The concept is based on good engineering practices pioneered by other industries (automotive, high tech)
- Benefit of identifying and fixing issues early - cost of correcting design and construction issues increases through the construction and start-up process
- ASTM E2500 enables issues to be identified and corrected early (Cost of correcting design and construction issues increases as construction and start-up processes continue)

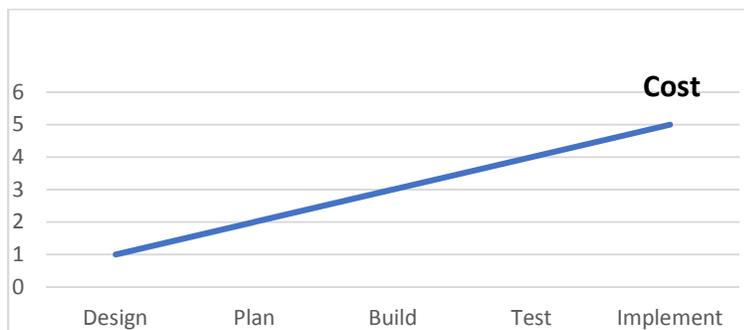


Figure 1: Cost to remedy a discrepancy rises as project progresses.

5.2 Desired CQV Process Functionality:

- Manage/share/leverage common data (equipment specs, drawings, protocols, design, risks)
- Ability for external service providers (engineering services, vendors) to access & enter CQV data directly
- Ability to establish and track phase - based testing, based on approved plan
- Ability to establish early on design/build issue identification and remediation
- Ability to auto generate and dynamically maintain trace matrices (TMs)
- Ability to capture and leverage vendor data (FAT, SAT)
- Repository for ALL CQV information (engineering and vendor turn over data, testing etc.)

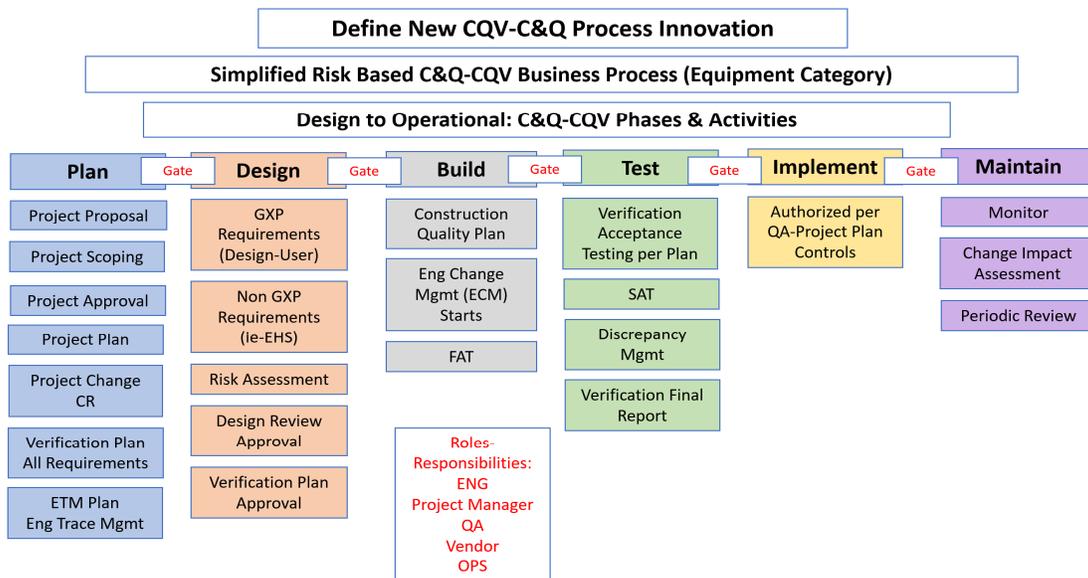
- eLibrary to manage requirements, risk assessments, test cases, designs
- Ability to generate standard system CQV document packs based on change impact assessment
- Flexibility to add/change/subtract CQV project items (projects in constant flux)
- Real time global accessibility to CQV project status information

6 Solution: Streamlined process supported by e-solution

Proposed Solution for Process Improvements

1. Adoption of a risk-based approach as outlined in ASTM E2500 and
2. Application of data centric eCQV system that enables:
 - Intelligent computer - aided electronic development and maintenance of project documentation
 - Electronic execution and assessment/utilization of project testing data
 - Risk-based approach decreases amount of testing performed during CQV, but increases controls needed for testing performed early in the process (Eng. Change Management & Data Integrity) to satisfy formal qualification requirements
 - eCQV solution provides controls in tandem with process improvements for productivity and flexibility

6.1 Proposed New CQV Process:



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6.2 Selecting an eSolution

Use an eCQV technology to embed the new lean and streamlined CQV process across the organization

The eCQV Solution selected and recommended to clients by Encova was Kneat Gx, the e-platform developed by Kneat Solutions. This recommendation was based on an in-depth evaluation of several systems against the Encova customers' functionality requirements. Kneat Gx scored highest, providing a comprehensive array of functionality with excellent performance with an intuitive user interface.

Functionality provided by the eCQV solution:

- Validation plan - change request impact checklist
- E-library structure (workspace)
- E-log master index (adding new equipment item(s))
- Generating required final "Pack of Documents" based on change request checklist
- ETM (Engineering Trace Matrix) Verification Plan (end to end tracking of tests by phase & responsibilities)
- Ability to establish and track phase-based testing based on approved plan
- VAL TRACE Matrix (automated linking and maintenance of Requirements, Design, Risk Assessment, Tests)
- e-Test Execution grid for data entry (Data Integrity & Part 11 Compliant)
- Auto generated Final Summary Report
- User role permission-based security architecture (allows controlled vendor data entry)
- Globally accessible status reporting & information access dashboard
- Flexibility to add/change/subtract CQV project items (projects in constant flux)
- Early on design issues identification, resolution & tracking

6.3 Benefits of the new CQV Approach

- Encova clients reported improvements using Kneat of over 60% cycle time reduction, and an increase in productivity of 90%
- Ability to Manage/Share/Leverage Common Data (Equipment Specs, Drawings, Protocols, Design, Risks)
- Ability for External Service Providers (consultants, Eng. services, vendors) to have controlled eCQV access to enter required Data (FAT, SAT) Directly (efficiently and compliantly)
- Ability to auto create TRACE Matrix and assign CQV testing based on risk assessment & phase
- Single repository for all CQV information including turn over package data, vendor specifications & testing
- Library of requirements, risk assessments, test cases, designs
- Ability to generate all required CQV "Pack of documents" related to Change Request Checklist
- Comprehensive E-log master index (adding new equipment item(s))
- CQV project item flexibility to add/change/subtract items (projects in constant flux)
- Provide real time globally accessible CQV project status & CQV information
- Phase appropriate testing based on approved plan (leveraging of data across all project phase)
- One Project-view Engineering (ETM) Test Matrix (verification plan matrix & change control management) (for change impact assessment, ability to modify test deliverables based on type/scope of equipment change)
- Early on identify & resolution of design/construction issues

One does not need to use a technology to gain process improvements. Applying a risk based, lean process such as ASTM 2500 will deliver process benefits. However, applying a suitable technology to capture this leaner process will provide significant productivity and cycle time benefits and make it fully leverageable and repeatable across the organization.

7 Customer Kneat eCQV Feedback:

Feedback	Feedback Category
Validation Work process cycle time reduced by 60%. Reduce number of steps, simplified collaboration and document closeout	Cycle time reduction
Change over team had 80% reduction in labor and change-over downtime	Productivity
<ul style="list-style-type: none"> • Personnel from other sites supported internal green field project in Europe without travel • QA person was traveling in China during the protocol close out, but able to remotely process without delay to document approval 	Global resource utilization-sharing-staffing improvements
Process Improvements: Document number log, document physical movement and status tracking, scanning of final document eliminated	Doc management logistics-improved control
Company employees can monitor external personnel activities real time to ensure compliance with company standards.	Vendor data entry-viewable
<ul style="list-style-type: none"> • RV performed prior to installation (construction phase) can identify an issue prior to costly installation of a defective or incorrect part. • IV performed prior to Mechanical Completion can prevent costly re-testing and fixes after the construction person has disbanded. 	Early-on issue identification-tracking
Control of Protocol pages and locking / storage of data is not possible in the paper world. There is a risk of data manipulation in the paper work. Date and time stamping in Kneat eliminates back dating or data loss.	Data integrity
Old system was paper based and required manual moving document one person to the next. First reviews did not see final document.	Improved collaboration for doc development, review/approval
The real-time collaboration and document organization greatly reduced the review and approval time required by Quality. Quality personnel were able to review documents during execution and were able to quickly find supporting documentation they need to approve the document. Paper based system would have delayed the start of manufacturing.	Cycle time reductions. Schedule Assurance
Project Manager was skeptical of using Kneat for a major project. After completion of the project the manager stated that the project would have been delayed if not for the use of the Kneat software.	Cycle time reductions, Schedule assurance
CQV Contracting company uses Kneat to perform thermal mapping projects for various clients. Clients and project personnel are not always at the same site. The projects are more efficient with Kneat, since all project members can access the documents from any location and can collaborate real-time to get issue resolved and documents closed.	Use of Kneat for thermal mapping project

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