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Integrated Commissioning and Qualification:

Saving Time and Money Without Compromising Quality

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Commissioning and Qualification Models – A Historical Perspective

How did we get here?

Overview

- Nomenclature
- Historical Perspective
- FDA Viewpoint
- 2 Models of C&Q
  - Benefits/Risks
  - Pitfalls

Nomenclature – Commissioning

- Commissioning is comprised of a combination of Installation/Operational Commissioning activities
- Equipment for which the IC/OC (frequently IV/OV) has been completed is considered "Commissioned"

Nomenclature – Qualification

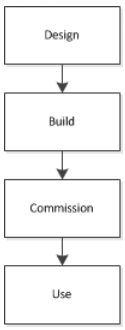
- Qualification is comprised of a combination of Installation/Operational Qualification activities
- Equipment for which the IQ/OQ has been completed is considered “Qualified”

- Note – Qualification work is frequently performed by a “Validation” group – causing confusion

Nomenclature – Validation

- Validation is comprised of a combination of Performance Qualification activities such as Cleaning Validation, Sterilization Validation or Process Validation
- Equipment for which the PQ has been completed is considered “Validated”

“A long time ago in a galaxy far, far away....”



Plants and Equipment were designed, then built

Designing engineers were responsible for making it all work – in commissioning

Then the plants and equipment were used to make products

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7

Pitfalls with the “old way”

- The quality of the work varied from plant to plant and from project to project
- Some teams did more exacting work, others did less
- If done poorly enough, poor design, implementation and startup would affect the quality of the products being made.

Commissioning costs were low, under 5% of total project cost

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8

FDA Response

Historically, when these types of situations arise, the FDA response is predictable:

"It is not the proportion of manufacturers who are in compliance …but the number who are out of compliance and whose noncompliance justifies regulatory action that necessitates making…regulations binding"

– FDA, 29-Mar-79 (Justification for cGMP's)

Note – Thus guidance has been superseded by the Jan 2011 guidance

FDA Response

FDA Issued the Guideline On General Principles Of Process Validation - May, 1987:

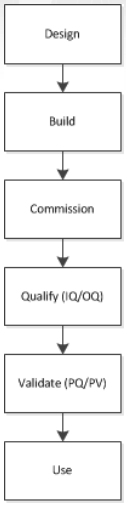
Defined Validation as – "Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its pre-determined specifications and quality attributes"

End Result – Models for C&Q

The model the FDA recommended in 1987 evolved into the now-typical IQ/OQ/PQ model

Validation groups were now charged with assuring that equipment was installed properly, operated properly and made product that met all specifications in a consistent manner

Model 1 – Qualify after Commissioning



IQ/OQ and PQ steps were responsible for ensuring that the equipment was installed, operated and made production in accordance with the specifications

This increased the documentation requirements for C&Q as the specifications were the basis for IQ/OQ and PQ

Model 1 – Benefits/Risks

All changes required per commissioning are implemented prior to onset of change control

Unless changes are rigorously tracked, the design specifications may not reflect the as-built system

Model 1 – Pitfalls

This led the industry to complete testing during commissioning and then follow up with a complete repeat of all testing again under IQ/OQ and PQ

This model led to Quality driven projects at the expense of Time and Cost

C&Q costs could be as high as 20-25%

- Discuss Case Study – Change Management

When Disaster Strikes

C&Q costs more than doubled – But – there were unwanted side effects:

- Documentation and C&Q change management models were still being developed
- Design drift led to IQ/OQ and PQ failure
- Immense project delays

Effective costs rose to over 30% – Discuss case Study

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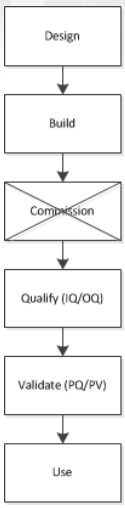
Model 2 – Skip Commissioning



As the costs of IQ/OQ and PQ increased, some companies started to cut back on commissioning in favor of Validation

The logic was that if Validation was going to test it all, why bother commissioning it?

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16

Model 2 – Risks

In this model, Validation ensured and documented that equipment met specification

However, making sure the equipment worked correctly could get lost…

Given that change control was linked to completion of qualification, this led to a situation where the systems do not work properly, but where change control and revalidation was required to fix the issues

Model 2 – Pitfalls

This led to a “Band-Aid” or “It is Good Enough” approach where issues were resolved procedurally instead of being properly fixed

This model led to Timeline driven projects at the expense of Quality and Cost

When Disaster Strikes

This model lowered C&Q (by removing commissioning) – But – there were unwanted side effects:

- Increased maintenance costs
- Lost batches
- Immense Change Control Costs

The lower costs of C&Q (~15%) were overshadowed by these consequences – Discuss case Study

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19

Where do we go from here?

How do we deliver Quality systems without blowing the budget or overrunning the schedule?

How do we set up a C&Q Programs that work?

What can we learn from the past?

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20

Overview

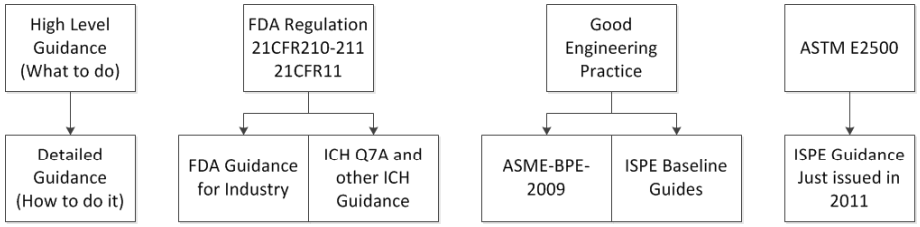
- What is ASTM E2500
- Reality Check – The Continuum
- Commissioning Change Management and Commissioning Protocols
- Two New C&Q Models
- Conclusions
- Acknowledgements

What is ASTM E2500?

- It describes an updated approach toward C&Q that is significantly different than previous models
- It uses a risk-based methodology to focus efforts in areas with the greatest impact to product quality and patient safety
- It is blissfully short (under 5 pages)

What is ASTM E2500?

- But, like many high level guidance's – It does not provide specific guidance:



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23

What is the Philosophy?

- We commission *everything* - If it is important enough to specify, it is important enough to test
- A scientific logical approach needs to be taken toward weighing risk and then designing equipment to mitigate that risk
- The more potential impact – The more time should be spent in ensuring that it was installed/operated correctly (more time verifying product contact surfaces and less time on instrument air lines).

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24

What is the Philosophy?

- There is nothing special about “Validation”, what matters is that you tested it and did so after the attribute has been properly started up and adjusted
- The starting point follows ICH Q8 whereby a product is dissected into a series of product Critical Quality Attributes and Critical Process Parameters used to control it
- What does this all mean – Present example

What is the Philosophy?

- Each step in the process is designed to ensure that all CPP’s are achieved.
- Critical Aspects that are used to control CPP’s are the Critical Aspects (components, instruments, process control elements, alarms, data, etc.) are then identified and designed in accordance with ICH Q9

Rubber Meets the Road

- ASTM E2500 officially does away with the traditional IQ/OQ/PQ model (and even the terms Commissioning, Qualification and Validation – lumping them together as “verification”)
- However, the reality is that the IQ/OQ/PQ model is still the norm in the industry and meets regulatory expectations

- EMEA, Annex 15, Section 4, 2001
- ICH Q7A, Section 12.3, 2001

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27

The Continuum

However - there is a vast grey area between the extremes of full IQ/OQ/PQ vs. full ASTM E2500

People who Require We Commission Everything Followed by A Full IQ/OQ/PQ

The Rest Of Us
(Someplace in the middle)

People who Require We Perform Fully Integrated Verification per ASTM E-2500

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28

When Disaster Strikes

All integrated C&Q models require that a project follow Good Engineering Practices and that the number of changes during C&Q are small.

If the design is off and/or if the Change Management scheme is weak all models all break down

When Disaster Strikes

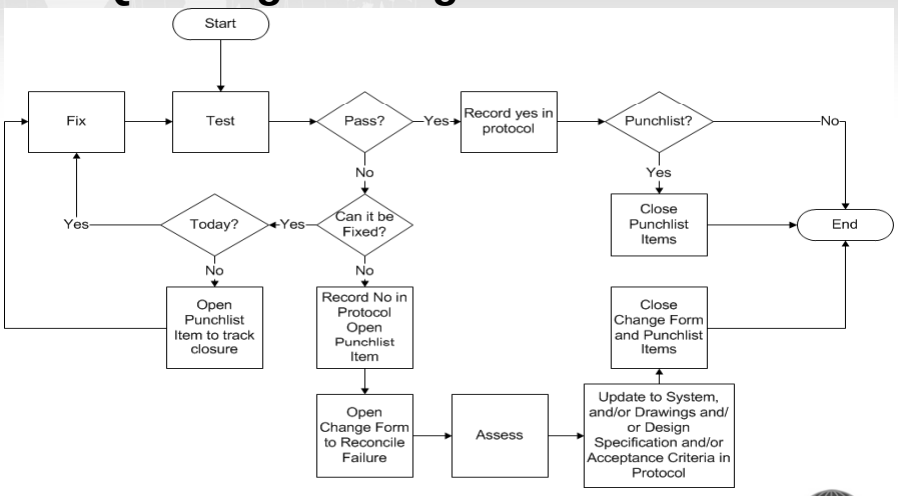
This results in

- Large Project Delays and Cost Overruns
- Ugly C&Q packages that lead to re-execution

Any lower costs of C&Q will be overshadowed by these consequences – Discuss case Study

Take Home Lesson – You Need Strong C&Q Change Management Scheme

C&Q Change Management



Path Forward

- There are many ways to implement integrated C&Q
- The following slides present two models that have proven to successful

Model 1 – The "Repeat Protocol Model"

- Perform an analysis to assess the level of commissioning required by each aspect
- Write and execute commissioning protocols to collect the data that supports that the systems work and has clear references to the design intent
- Use the Commissioning Change Management System
- Summarize the work in reports

Model 1 – At IQ/OQ

- For IQ/OQ, retitle the commissioning protocols and modify to use the corporate Validation Discrepancy System
  - Review the Commissioning package. If the data was good and well documented with signatures and dates, enter the reference into the IQ/OQ
  - If there were any gaps, or if there were issues in commissioning, execute those protocol sections
- Summarize the work in reports

Model 1 – Benefits/Risks

Validation can choose to expand testing at IQ/OQ as needed (perhaps revisiting a subset of some test classes such as slope checks or I/O checkout) without needing to generate new protocols or lengthy justification

IQ/OQ execution will be a lengthy paper chase, but the end result is high-quality traceability matrix from requirements through Commissioning to Qualification

Model 1 – A Case Study

- How did this model work?
- How much time did this save?
- How did the final documentation package look at inspection?

Model 2 – The "Risk Based Scheme"

- Perform an analysis to assess the level of commissioning required by each aspect
- Write and execute commissioning protocols to collect the data that supports that the systems work and has clear references to the design documents and Critical Aspects
- Use the Commissioning Change Management System
- Summarize the work in reports

Model 2 – At IQ/OQ

- For IQ/OQ, perform an audit of the commissioning package and using the Critical Aspects traceability matrix guide the testing.
- As an example:
  - Reverify challenges tied to CPP's
  - Challenge any aborting or holding alarms
  - Test an AQL of other aspects
  - Test any portions that caused issues in commissioning
- Summarize the work in reports

Model 2 – Benefits/Risks

IQ/OQ execution should be fast (assuming commissioning did its job) and will result in a package that demonstrates that that everything was properly commissioned and that all CPPs were achieved

Validation will need to develop *de novo* protocols and justify the selection logic.

Model 2 – A Case Study

- How did this model work?
- How much time did this save?
- How did the final documentation package look at inspection?

What Happens if you Implement Full E2500

- How would this work?
- How much time would this save relative to the other two models?
- How would the final documentation package look at inspection?

When do we Test?

- Materials of construction do not change. Verifying that a product contact surface is suitable can be done at any time – There is no need to wait for IQ
- Ability to control pressure does change, Verifying the operating pressure range must occur after the tuning has been established – There is no need to wait for OQ
- Bottom Line – Be Smart and Don't Repeat Good Testing

Tips on Commissioning Protocols

- Write protocols where the verification tables have the acceptance criteria at the top – allows testers to simply answer yes or no
- Generate short, photocopiable data sheets with the acceptance criteria to accompany repetitive tests – allows testers to repeat as required, justify why a run was acceptable and if not, what was changed
- Limit the number of times per page a tester needs to initial and date

Tips on Compliance

- The easier you make it for an Engineer to be compliant, the more likely they are to deliver a leverageable GMP package
- The easier it is to document changes, the more likely changes will get documented and the lower the chance that the documents get out of sync with the system

Conclusions

Using Integrated/Risk-Based C&Q can help deliver a quality plant while saving time and money

If you set up C&Q systems where it is easy to be compliant, your packages will be clean and professional

ASTM E2500 is a good framework, but avoid getting hung up in the Philosophy – Do the right thing

Lessons Learned (the hard way)

- Schedule Numerous Design Reviews
- It is critical that there is a clean handoff from design to construction to commissioning and to qualification – No tossing it over the wall
- Try not to outsource commissioning – Doing so wastes a training opportunity
- Controls, Validation, Engineering and Manufacturing need to partner for success

Acknowledgements

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