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Integrated Commissioning and Qualification:

Saving Time and Money Without Compromising Quality

About the Speaker

- Jack Greene is an independent consultant with over 15 years of Commissioning and Qualification, Plant-Wide Automation Design, Continuous Improvement and Compliance experience in the biologic API, oral solid dosage and parenteral drug product area.
- Jack's extensive background and experience in the Pharmaceutical industry includes previous positions as QC Chemist, PLC/DCS Architect and Quality Engineer. He is an expert in helping scientists and engineers express complex issues such that they can be understood by non-technical people. He has worked at Eli Lilly& Co, Alnara Pharmaceuticals, Altus Pharmaceuticals, Alkermes, Genzyme and Ares-Serono.

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Commissioning and Qualification Models – A Historical Perspective

How did we get here?

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Overview

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

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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”

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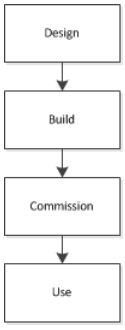
“A long time ago in a galaxy far, far away....”



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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SW1

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 10% of total project cost

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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)

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Slide 9

SW1 I think your 10% cost is overstated. For this model it was probably less that 5%. Today pure commissioning cost for decent sized projects should be in the 2-4% range depending on mechanical system complexity

Steve, 12/7/2011

SW2

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”

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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

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Slide 11

SW2 Please note that that this guidance is now withdrawn and has been replaced by the new PV Guidance issued on January 2011

Steve, 12/7/2011

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

SW3

This increased the documentation requirements for design phase as the specifications were the basis for IQ/OQ and PQ

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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

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Slide 13

SW3 Did you mean qualification testing phase. GEP would have required all identified design elements to have an associated specification. At this time all specifications were tested (or retested after comissioning) since there was no means to focus on things that impact product quality (CQAs)
Steve, 12/7/2011

Model 1 – Pitfalls

This led the industry to complete testing during commissioning and then follow~~ing~~ 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 30% SW4

- Discuss Case Study – Change Management

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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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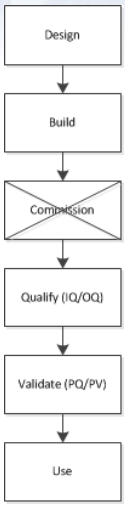
Slide 15

SW4 This is a high extreem; more likely in the mid-teens to low 20's
Steve, 12/7/2011

SW5

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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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

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Slide 17

SW5 I do not agree with this assumption. As a part of contractual project close-out and turnover to the owner the CM needed to perform commissioning. Qualty and Validation groups looked on the an an engineering (only) related activity and chose to ignore it for thier purposes and just relied on the validation effort conducted after the engineering "threw it over the wall"

Steve, 12/7/2011

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

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When Disaster Strikes

This model lowered C&Q costs dramatically – But – there were unwanted side effects: SW6

- 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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Slide 20

SW6 Somewhat disagree. The point here is that the C cost was now burried in the Project engineering budger and only the Q cost was included in the Validation Budget. Therefore is was a false reduction because the budget comparison basis changed

Steve, 12/7/2011

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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Overview

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

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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 ~~the product~~ product quality and patient safety
- It is built upon many hybrid methodologies from the industry
- It is blissfully short (under 5 pages)

SW

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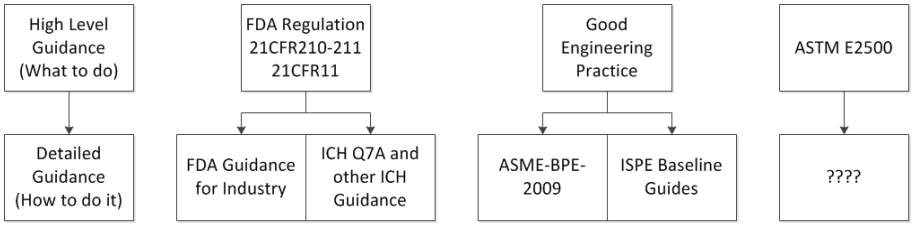
SW8

What is ASTM E2500?

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



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Slide 23

SW7 I was on the drafting team for this standard and I do not agree with this bullet. It is built on QRM/ICHQ9 as applied to C&Q to provded commerical manufacturing facilities that are fit for intended use

Steve, 12/7/2011

Slide 24

SW8 Related to the ASTM box, ISPE and issued to new guidance documents this year. One focuses on how to implement for ASTM and the other adresses transitional QRM approachs to move form old BG5, Impact Assessment to ASTM

Steve, 12/7/2011

What is the Philosophy?

- A scientific logical approach needs to be taken toward weighing risk (we do not need to test everything, only what matters) SW9
- 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) SW1
- There is nothing special about “Validation”, what matters is that you tested it and did so after the attribute became fixed.

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What is the Philosophy?

- ASTM recommends the approach from ICH Q8/Q9 whereby a product is dissected into a series of Critical Quality Attributes SW
- Each step in the process is scrutinized and linkages to CQA’s defined and documented paying attention to environment, equipment, instruments controls, and analytical QC tests

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Slide 25

SW9 This in not correct. Risk assessment has nothing to do with what is tested. Under GEP and commissioning everthing is tested. Risk assessment is used to identify the Critical Aspects, that control the CPPs, that assure final CQAs are achieved in production. The identicied CAs are the focus for qualification. The testing for the CAs done during commissioning/verification is summarized in summary reports for ASTM or can be leveraged into IQ/OQ.
Steve, 12/7/2011

SW10 This also is not correct. The goal here is transparency. There should be no difference between GEP and GMP testing. The only diffenence is how it is documented and whether it is subject for Change Control of Engineering Change Management through the balance of the product Lifecycle.
Steve, 12/7/2011

Slide 26

SW11 Q8, Product and Process knowledge (science) provide the basis for Product User Requirements, CQAs. We look at each (major) step of the manfacturing process and idnetify the CPPs associated with that step. Then we apply QRM/
ICH Q9 to identy the controls (CAs). The CAs can be comprised of components, instruments, process control elements, alarms, data, (or procedures) that are ultimately verified
Steve, 12/7/2011

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 is considered mandatory by some regulatory bodies SW1

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

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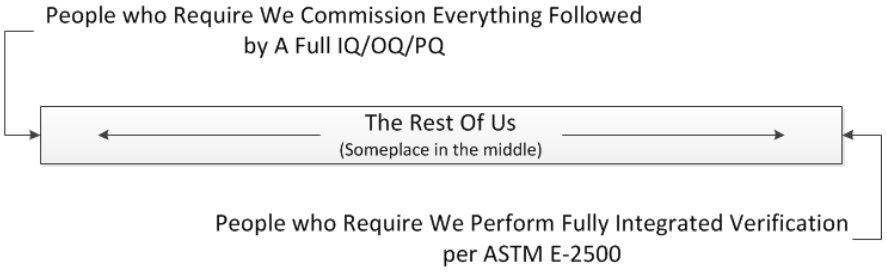
The Continuum

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



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Slide 27

SW12 This is not correct. You have referenced "Guidance Documents" and not Regulations. Annex 15, 2001, noted that IQ OQ PQ were acceptable isdustry practices at that time. They are still acceptable but are neither mandatory nor is there any requirement in the Annex that these docuemnts require pre or post approval.

Same with ICH Q7A, 2001.

Note the new FDA PV Guideance,2011, references ASTM as an acceptable appraoch for qualification.

Note that Pfize is currently implementing a number of projects in Europe that are not using IQ OQ.
Steve, 12/7/2011

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 (< 5%). SW15

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

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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

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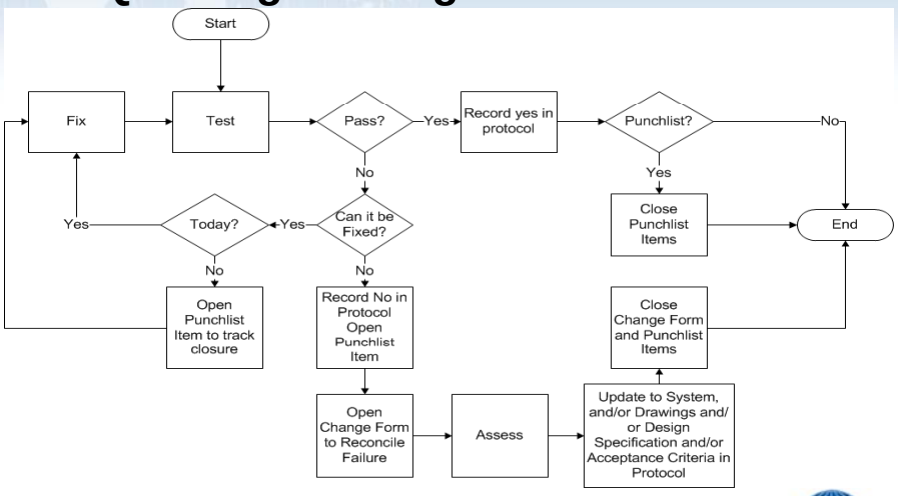
Slide 29

SW15 This is not the case. The need is to have a sufficiently robust Change Management System in place. What is the basis of the 5%?

Steve, 12/7/2011

C&Q Change Management



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Path Forward

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

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Model 1 – The "Repeat Protocol Model"

- Perform a science based risk analysis to assess all of the items that require commissioning SW16
- Write and execute commissioning protocols to collect the data that supports that the systems work and has clear references to the design documents
- Use the Commissioning Change Management System
- Summarize the work in reports

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Model 1 – At IQ/OQ

- For IQ/OQ, retitle the commissioning protocols and modify to use the corporate Validation Discrepancy System SW17
  - 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

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Slide 33

SW16 As per earlier comment, risk has no relationship to what is tested. GEP mandates everything is tested. The Risk analysis provides the focus for that testing that is leveraged for qualification.
Steve, 12/7/2011

Slide 34

SW17 Why is this required? By both ASTM and REqulatory defination QA change control is not required until qualification is complete
Steve, 12/7/2011

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

SW18

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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?

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Slide 35

SW18 Not is a documentation management scheme is proactively put in place
Steve, 12/7/2011

Model 2 – The "Risk Based Scheme"

- Perform a science based risk analysis to assess all of the items that require commissioning SW19
- 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

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Model 2 – At IQ/OQ

- For IQ/OQ, perform an audit of the commissioning package and use a risk assessment to guide the testing. SW20
- As an example:
  - Reverify challenges tied to CPP or KPP SW21
  - Challenege any aborting or holding alarms
  - Test an AQL of other aspects
  - Test any portions that caused issues in commissioning
- Summarize the work in reports

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Slide 37

SW19 Not correct, have discussed previously
Steve, 12/7/2011

Slide 38

SW20 I would change "risk assessment" to "CA tracability Matrix"
Steve, 12/7/2011

SW21 I suggest CQA and CPP instead. KPP is not used in ICH Guidance. It has be picked up by some in industry and defined differently by those using it
Steve, 12/7/2011

SW22

Model 2 – Benefits/Risks

IQ/OQ execution should be fast (assuming commissioning did its job) and will result in a represented, risk based should have ensured that everything is working and

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

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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?

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Slide 39

SW22 This slide is confusing, I do not understand
Steve, 12/7/2011

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?

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What do we Test? SW23

- Once all of these aspects have been mapped to CQA's, the risk can be evaluated and documented
- A design review is used to map the system to the CQA's to rationally determine what to test
- This is not easy, but in the long run, it links the equipment test strategy to the science behind the manufacturing process

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Slide 42

SW23 Again, everything is tested. Another example: a plant steam system vs. a clean steam system. The latter has product quality/patient safety impact (High Risk). The former no direct product/patient imnpact (Low Risk). BOTH have an engineering based design specification for operating pressure, both are commissiomned/tested, both must meet the acceptance criteria.
Steve, 12/7/2011

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

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What do we Test? SW24

- The inside of a the process vessel needs more scrutiny than the outside
- Sanitary piping needs more scrutiny (L/D, slope checks, MOC) than condensate drains (slope)
- Instruments and controls that confer quality (pH control in a bioreactor or flow control in HPLC) need more scrutiny than those that measure process performance

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Slide 44

SW24 The question here is not "What do we Test". The question is what is the extent of the documentation supporting the testing effort and "formal" requirement for a second SME review.
Steve, 12/7/2011

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

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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

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Conclusions

Using Integrated 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

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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

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Slide 47

SW25 I would change Integrated to Risk Based
Steve, 12/7/2011

Acknowledgements

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