Commissioning and Qualification Baseline Guide Volume 5 – 2nd Edition

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CAI

C&Q CoP
ISPE Webinar
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Today’s Speakers

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Commissioning Agents, Inc.

Steven is Principal Consultant for CAI Consulting and has more than 35 years’ experience in the pharmaceutical, biotech, and device industries. Prior to joining CAI, he was Senior Associate and Director of Compliance for IPS, Senior Consultant for Drug and Device Associates and has served in manufacturing facility and corporate senior management roles at Sterling Drug and Bausch & Lomb.

Steve served for four years as chairman of the ISPE Community of Practice for Commissioning and Qualification and was on the ISPE task team that developed the ASTM E2500 Verification Standard. In addition, he served as a leader of the Task Team that produced the ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment, and was a leader the Task team that developed the ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification. Most recently, Steve was the co-lead for developing the Baseline Guide Vol 5: Commissioning & Qualification 2nd Edition to incorporate QRM approaches.
Topics for Today:

- 2\textsuperscript{nd} Edition Guide Benefits
- 2\textsuperscript{nd} Edition summary and comparison to original Baseline Guide 5
- Quality Risk Management and the core C&Q relational model
- Supporting practices necessary for C&Q success
2nd Edition Benefits
New Guide Benefits

- URS definition including “fitness for use” and differentiate requirements (what) from specs (how) and distinguish between product quality impact and no quality impact

- Risk Assessment to identify Critical Design Elements (CDE's)

- An optimized Design Review/Design Qualification process, focused on the CDE's

- A clear C&Q planning process, including a Document Approval Matrix

- A streamlined structure in how to execute the testing, including engineering and quality differentiation and testing phase minimum requirements for completion
Critical Design Element (CDE) – Definition

• Design function or feature of an engineered system that is necessary to consistently manufacture products with the desired quality attributes.
  - Examples of automation design functions include alarms and data management.
  - Examples of engineering design features include components, instruments, and materials of construction.
• CDEs are identified and documented based on technical understanding of the product CQAs, process CPPs, and equipment design/automation.
• CDEs are verified through C&Q.
New Guide Benefits (continued)

- The traceability matrix as a project management tool
- A streamlined, risk-based approach to periodic review
- Supplier verification and acceptance with minimal testing repetition
- Differentiates engineering change management from operational change control
- Contemporary/simply examples for all steps of the C&Q process
2nd Edition Guide Summary
Revised Guide – 14 Chapters

1 – Introduction
2 – User Requirement Specification
3 – System Classification
4 – System Risk Assessment
5 – Design Review and Design Qualification
6 – C&Q Planning
7 – C&Q Testing and Documentation
8 – Acceptance and Release
9 – Periodic Review
10 – Vendor Assessment for C&Q Documentation Process
11 – Engineering Quality Process
12 – Change Management
13 – Good Documentation Practice for C&Q
14 – Strategies for Implementation of Science and Risk-Based C&Q Process
Revised Guide – 17 Appendices (link to chapters)

1 – Regulatory Basis
2 – User Requirements Specification Example
3 – System Classification Form Example
4 – Direct Impact System Examples
5 – System Risk Assessment Example
6 – Design Review/Design Qualification Examples
7 – Supporting Plans
8 – System Start-Up Examples
9 – Discrepancy Form Example
10 – Qualification Summary Report Examples
11 – Periodic Review Example
12 – Period Review for Controlled Temperature Chambers
13 – Vendor Assessment Tool Example
14 – Organizational Maturity Assessment Example
15 – Approach to Qualifying Legacy Systems or Systems with Inadequate Qualification
16 – References
17 – Glossary
In 2001, the ISPE C&Q Baseline Guide was published. Drivers at the time…

- Cost and time required to bring facilities on line had been increasing, in many cases due to inconsistent interpretation of regulatory requirements.
- ISPE and Industry partnered with the regulators to enhance understanding of facility baseline CGMP requirements.
- BG5 Guide was intended to define key terms and offer consistent interpretation, while still allowing a flexible and innovative approach to facility design, construction, commissioning and qualification.
- Goal of the Guide was to provide value added guidance to the industry that will help facilitate timely and cost-effective facility C&Q
Times have changed in 18 years. What drove the revision?

- Focus is on Quality by Design, and on risks to product quality
- Industry and Regulators have moved to a science and risk-based qualification approach
- The revised Guide recognizes current best practices for C&Q at companies and combined concepts included in regulatory agency guidance (e.g. EU, FDA, ICH) and the published ISPE documents:
  - ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification
  - ISPE Good Practice Guide: Applied Risk Management for Commissioning and Qualification
- This Guide revision supersedes these documents.
Poll Question #1

Has your organization been using the older version of these guides?

A. 2001 ISPE Baseline® Guide: Volume 5 – Commissioning and Qualification
B. ISPE Guide: Science and Risk-Based Approach for the Delivery of Facilities, Systems, and Equipment
D. A combination of A & B or A & C
E. None
Leverages the best of these three guides and brings them to contemporary standards:

- Focus on a compliant, efficient and cost-effective approach.

- Focus on the qualification of “Critical Design Elements”:
  - System functions and features that have been identified as having impact on product quality, and control risks to ensure patient safety.

- Focus on the approach, and do not get hung up with terminology (C&Q, Verification, IV/OQ, etc).
  - C&Q is used to describe the process for establishing that facilities, systems and equipment are fit for purpose
  - Verification is used to describe an activity performed during the C&Q process to establish suitability for intended use

- The Revised C&Q Baseline Guide will replace the current guidance which will be retired when this guide is published.
The difference between the revised guide and the old one

• Focuses on Critical Design Elements (CDE’s) and Critical Process Parameters (CPP’s) which provide the ability to deliver Critical Quality Attributes (CQA’s)
• Provides guidance on how to apply the Quality Risk Management (QRM) process to C&Q, to establish Critical Design Elements (CDEs), which are subject to qualification
• Clarifies User Requirements, Design Review (DQ), and System Acceptance and Release
• Recommends an integrated C&Q approach, that begins at the Design Phase
• Clarifies Change Management processes required to support the C&Q process
• Recognizes current industry best practices
• Provides GEP documentation standards
Draft Team Companies Represented

Akebia
Amgen
Pfizer
CAI
IPS
Alnylam
Bayer

Cook Medical
J and J
Abbvie
GSK
Merck
FVCS
Rentschler
How do we make the C&Q process...

• Superior
• Faster
• More Efficient
Process Overview

Inputs to C&Q Process
- Product Risk Assessment/Control Strategy (ICH Q8)
- CQA
- CPP
- Regulatory, Organizational, Site, Operational, and Health/Safety/Environmental Requirements

Define Requirements
- System Classification
- System Risk Assessment

Design Specify
- DR/DQ

Build/Verify
- Traceability
- C&Q Testing and Documentation
- Acceptance and Release

Accept and Release
- Operation

Periodic Review
- Continued Improvement
Terminology / Glossary

Defined Terms:
- “Commissioning”
- “Qualification”
- “Commissioning and Qualification”
- “Validation”
- “Verification”

Retired Terms:
- “Indirect Impact”
- “Component Critically Assessment”
- “V-Model”
- “Enhanced Documentation”
- “Enhanced Commissioning”
- “Enhanced Design Review”
- “Leveraging” (now “integrated C&Q process”)
Define Good Engineering Practices…….

Use the engineering deliverables to produce documented evidence that systems are:
- Installed to meet the specifications
- Operate to meet the specifications

Align level of C&Q effort with level of risk
- (Quality and Business)

Remove artificial constraints
Quality Risk Management
The core C&Q relational model
Use System Risk Assessment to:

- Define the equipment/system risks to product quality
- Define the risk controls (Critical Design Elements – CDEs)
- Define which instruments/alarms are critical with supporting rationale
- Link required testing to product process/quality controls
- Provide logic to qualification
System Risk Assessment Process Relationship Diagram

Subject Matter Experts
- Process
- Product
- System
- Regulatory
- Quality
- Vendors

User Requirements Specification

System Risk Assessment

Commissioning/Testing

Acceptance and Release Report

Next Validation Stage/Operations

Design Specifications

Design Review/Design Qualification

Vendor Assessment

Feed into ongoing maintenance management systems

• Vendor Documents
• Good Engineering Practices
• Change Management

Traceability
System Risk Assessment (SRA) Approach Benefits

- Helps identify design solutions to meet ‘Requirements’
- Provides a quality focal point for the design review process (DQ)
- Focuses Quality/Validation on product quality/CDEs
- Defines the ‘controls’ in place around the identified risks
- Provides a ‘C&Q focus’ to ensure the identified controls are in place and tested
- Establishes a traceability tool from the Qualification Summary to the various lifecycle activities and testing
Chapter Highlights

- User Requirement Specification
- System Classification
- Design Review and DQ
- C&Q Planning
- C&Q Testing and Documentation
- Acceptance and Release
- Periodic Review
- Vendor Verification Documentation Assessment
- Engineering Quality Process (EQP)
- Change Management
- Good Documentation Practice
- Strategies for Implementation of Science and Risk-Based C&Q Process
Use Requirement Specifications

- Define “Intended Use”
- Separate Quality requirements from other requirements
- Written to be verifiable
- Do not define “how”

<table>
<thead>
<tr>
<th>ID No</th>
<th>Requirement</th>
<th>Type</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td><em>This is an appropriate requirement (for a granulator):</em> &lt;br&gt;The system must be capable of a chopper speed range of 1500 and 3000 rpm ± 10 %.*</td>
<td>SME</td>
<td>Product and process requirements</td>
</tr>
<tr>
<td>2.</td>
<td><em>This requirement is not appropriate:</em> &lt;br&gt;&lt;The vendor should supply appropriate Operation and Maintenance manuals, with adequate drawings for operation, maintenance and troubleshooting in English.*</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Why: *This is not a requirement of the system; it should be included in contract documents or engineering specifications.*
Data Sources Used to Develop the User Requirement Specifications

- Product and Process Development Phase:
  - CQAs
  - CPPs
  - CAs
  - GMP Regulatory Requirements
  - Organization Quality Requirements

- Requirements and Design Phase:
  - URS
  - System Risk Assessment
  - Design Specifications
  - National, Local, and Site Requirements
  - Business/ HSE/Owner/ SME Requirements
  - Engineering Specifications and Industry Standards
System Classification

- First cut to identify systems with direct product quality impact
- Based on system boundaries for integrated testing
- Updated the “Questions” methodology

| Q1 | Does the system contain CAs/CDEs or perform functions that serve to meet one or more process requirements (CQAs) including CPPs? |
| Q2 | Does the system have direct contact with the product or process stream and does such contact have the potential to impact the final product quality or pose a risk to the patient? |
| Q3 | Does the system provide an excipient or produce an ingredient or solvent (e.g., WFI) and could the quality (and compliance with the required specifications thereof) of this substance impact the final product quality or pose a risk to the patient? |
| Q4 | Is the system used in cleaning, sanitizing, or sterilizing, and could malfunction of the system result in failure to adequately clean, sanitize, or sterilize such that a risk to the patient would result? |
| Q5 | Is the system used in cleaning, sanitizing, or sterilizing, and could malfunction of the system result in failure to adequately clean, sanitize, or sterilize such that a risk to the patient would result? |
| Q6 | Does the system use, produce, process, or store data used to accept or reject product, CPPs, or electronic records subject to 21 CFR Part 11 [20] and EU GMP Vol. 4, Annex 11 [21] or the local equivalent? |
| Q7 | Does the system provide container closure or product protection, the failure of which would pose a risk to the patient or degradation of product quality? |
| Q8 | Does the system provide product identification information (e.g., lot number, expiration date, counterfeit prevention features) without independent verification or is the system used to verify this information? |
Design Review Culminates in DQ

Design Review:

1. Designate DR Lead (per plan document)
2. Form DR Team (include system owner, SME, engineering, quality)
3. Define the Scope and Boundaries of the Review
4. Review the Design Requirements (URS/Traceability Matrix) against Design Documents
5. Summarize Acceptability of the Design
6. Evaluate Summary Questions and Resolve Gaps
7. Approve Report
Design Review Culminates in DQ

Design Qualification:

1. Identify Scope of System
2. System URS
3. Completed DR Report(s)
4. Design Documentation
5. Verify CAs/CDEs and Quality/Regulatory Requirements
6. Document Traceability and Acceptance Criteria
7. Approve DQ (Summary Report)
## C&Q Planning – Documentation and Approval

<table>
<thead>
<tr>
<th>Document</th>
<th>Pre-Approvers</th>
<th>Post-Approvers</th>
<th>Typical Document Preparation</th>
<th>Chapter Reference</th>
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</thead>
<tbody>
<tr>
<td>C&amp;Q Plan</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td>Technical Chapter 6</td>
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<tr>
<td>User Requirements Specification</td>
<td>Not applicable</td>
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<td>Technical Chapter 2</td>
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<td>System Classification</td>
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<td>Technical Chapter 3</td>
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<td>System Risk Assessments</td>
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<td></td>
<td>Quality Chapter 4</td>
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<tr>
<td>Design Review</td>
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<td></td>
<td>Technical Chapter 5</td>
</tr>
<tr>
<td>Design Qualification</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td>Quality Chapter 5</td>
</tr>
<tr>
<td>Commissioning Testing documentation, (e.g., FAT, SAT)</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Technical Chapter 7</td>
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<tr>
<td>Qualification Testing Documentation where used</td>
<td>A</td>
<td>A</td>
<td>A</td>
<td>Quality Chapter 7</td>
</tr>
<tr>
<td>Turnover Package</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td>Technical Chapter 7</td>
</tr>
<tr>
<td>Commissioning Acceptance and Release Report</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td>Technical Chapter 8</td>
</tr>
<tr>
<td>Qualification Acceptance and Release Report (including Testing from Commissioning)</td>
<td>Not applicable</td>
<td></td>
<td></td>
<td>Quality Chapter 8</td>
</tr>
<tr>
<td>Traceability Matrix</td>
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<td></td>
<td>Technical Chapter 8</td>
</tr>
<tr>
<td>Vendor Assessment</td>
<td>Not applicable</td>
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<td>Technical Chapter 10</td>
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### C&Q Testing and Documentation

#### Documentation Terminology Comparison

<table>
<thead>
<tr>
<th>Document Type</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>Document Reviews</td>
<td>Confirming that the testing/inspection has been carried out and is recorded per agreed Good Documentation Practices standards (e.g., material certifications, vendor documentation)</td>
</tr>
<tr>
<td>FAT/SAT</td>
<td>Testing to demonstrate that a system meets established design requirements and contractual obligations... ...and requires vendor involvement and technical oversight</td>
</tr>
<tr>
<td>Testing and Balancing Reports</td>
<td>CAs/CDEs</td>
</tr>
<tr>
<td>Qualification</td>
<td>Quality Unit oversight</td>
</tr>
</tbody>
</table>
C&Q Testing and Documentation

Discrepancy Management

• Describes how to handle C&Q test results that do not meet the expected results or acceptance criteria.

• Discrepancies related to CAs/CDEs are critical and require Quality Unit approval prior to closure.
Acceptance and Release

- Qualification status is reviewed and accepted for next stage
- Quality system elements complete (SOPs, training, PM and cal program, TOPs)

Equipment or System

Functional Area
Periodic Review

Phase 1 – System Categorization / Schedule Assignment
- Regulations
- Product Quality Risk
- Monitoring

Phase 2 – Periodic Review Process
- Compliance expectations
  - Periodic requalification e.g. autoclaves/depyrogenation tunnels
  - Periodic review
- Changes
- Maintenance / Calibration
- Non-Conformance

<table>
<thead>
<tr>
<th>Periodic Review Category</th>
<th>Periodic Review Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>This category relies on existing Quality systems and performance monitoring programs; periodic review is not required, e.g. critical utility systems such as compressed air, Purified Water or WFI.</td>
</tr>
<tr>
<td>1</td>
<td>This category has established requirements from regulations specific to the system and is not subject to additional periodic assessment activities, e.g. autoclaves/depyrogenation tunnels.</td>
</tr>
<tr>
<td>2</td>
<td>Perform reviews at 2 year intervals.</td>
</tr>
<tr>
<td>3</td>
<td>Perform reviews at 3 year intervals.</td>
</tr>
</tbody>
</table>
Vendor Verification Documentation Assessment

- Is vendor testing/documentation reliable enough to support qualification?
- Assessment tool provided
Engineering Quality Process (EQP)

Relates Good Engineering Practices to QMS
Change Management Lifecycle
Good Documentation Practice

Relates testing documentation to *data integrity*:
- Attributable
- Legible
- Contemporaneously recorded
- Original or a true copy
- Accurate

Best Practices defined for GEP, GMP
Strategies for Implementation of Science and Risk-Based C&Q Process
Appendix – Tools, Templates, Examples

- Regulatory references
- URS example/template
- Direct impact system’s CQAs/CPPs
- Sample risk assessment (Process Air)
- Design review example/template
- Commissioning checklists
- Periodic review example/template
- Vendor document assessment tool
- Approval matrix
- And more!.....
## Changes to Key Processes have Resulted in Measurable Value

<table>
<thead>
<tr>
<th>Historical Approach</th>
<th>New Approach</th>
<th>Benefit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Quality protocols at project-end with testing redundant to engineering project lifecycle</td>
<td>Qualification process integrated into engineering project without unnecessary redundant testing</td>
<td>Efficient use of resources and reduced pressure on project schedule</td>
</tr>
<tr>
<td>Qualification testing based on equipment specifications and capabilities</td>
<td>Testing also considers critical controls, detection mechanisms &amp; all quality systems</td>
<td>Focuses qualification efforts on defined critical aspects</td>
</tr>
<tr>
<td>Design review applied inconsistently with unstructured Quality involvement</td>
<td>Design review well-directed with defined Quality involvement</td>
<td>Enables appropriate and defendable Quality oversight</td>
</tr>
<tr>
<td>Changes are not well controlled until a system is qualified and released for use</td>
<td>All changes are effectively managed throughout the engineering project</td>
<td>Prevents need to perform redundant testing at project-end</td>
</tr>
</tbody>
</table>

**Good Engineering Practices**

- **Risk Management**
- **Systematic Design Review**
- **Engineering Change Management**

**Benefit**

- Efficient use of resources and reduced pressure on project schedule
- Focuses qualification efforts on defined critical aspects
- Enables appropriate and defendable Quality oversight
- Prevents need to perform redundant testing at project-end
Thank you for joining me today!
Poll Question #2

How will your company implement QRM based C&Q?

A. Follow the principles of the 2\textsuperscript{nd} Edition Baseline Guide 5
B. Apply a different QRM based C&Q approach
C. Keep using our current Quality System for Qualification
D. Stick with original BG 5 V-Model approach with leveraging
Q&A

Contact Information

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Upcoming Webinars

• 24 September 2019 – Qualification of PAT Based Control Strategies for Batch and Continuous Manufacturing
• 16 October 2019 - The ISPE Pharma 4.0 Operating Model Introduction – Basis for the ICH Holistic Control Strategy

Topic Ideas or Feedback?
Send to ispeak@ispe.org

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