



Abbott

Turning Science Into Caring

Process Qualification – Linking C&Q to Process Validation

David Dolgin
Senior Quality Program Manager
Global Quality Systems
Abbott Global Pharmaceutical Operations



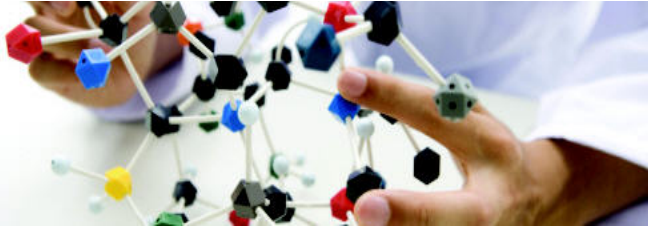
© 2011 Abbott





Topics

- Background on Commissioning & Qualification (C&Q)
- Risk-Based Approaches - ICH Q9 and ASTM E-2500-07
- FDA Process Validation Guideline – How it Fits
- Implications for Facility and System Design
- Transitional Approaches for Linking C&Q to Process Val
- Maintaining a Qualified State
- Some Real World Lessons



A Brief History of C&Q...

Validation Quality Systems have traditionally described two separate but related activities:

- **Qualification** of Systems and Facilities
- **Validation** of Manufacturing and Supporting Processes





Qualification – A Broken Process



- One-Size-Fits-All Approach
- Emphasis on Documentation – Not Process Requirements
- Absent or Incomplete Assessment of Risks to Product Quality & Patient Safety
- IQ/OQ More Intensive Than PQ
- Organizations Refused to Leverage Commissioning
- “Deviations” for Trivial Items
- “Change-is-Bad” Attitude Driven by Cost / Time Inhibited Innovation & Continuous Improvement



A Road Forward...



- ISPE Baseline Guide 5 (2001)
- “Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach” – FDA (2004)
- ISPE White Paper – “Risk Based Qualification for the 21st Century” (2005)
- ICH Q9 Quality Risk Management (2006)
- ASTM E 2500 “Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment” (2007)



ICH Q9 – Key Principles

- “The evaluation of the risk to quality should be based on scientific knowledge and ultimately link to the protection of the patient.”
- “The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.”

Guidance for Industry

Q9 Quality Risk Management

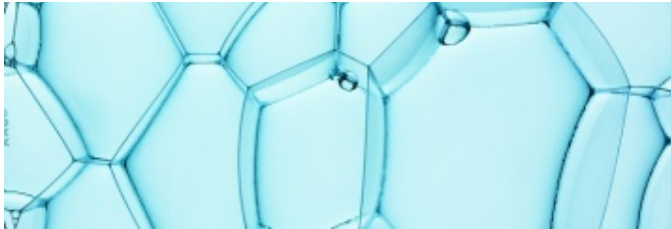
Additional copies are available from:

*Office of Training and Communication
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>*

*Office of Communication, Training and
Manufacturers Assistance, HFM-40
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike, Rockville, MD 20852-1448
<http://www.fda.gov/cber/guidelines.htm>*

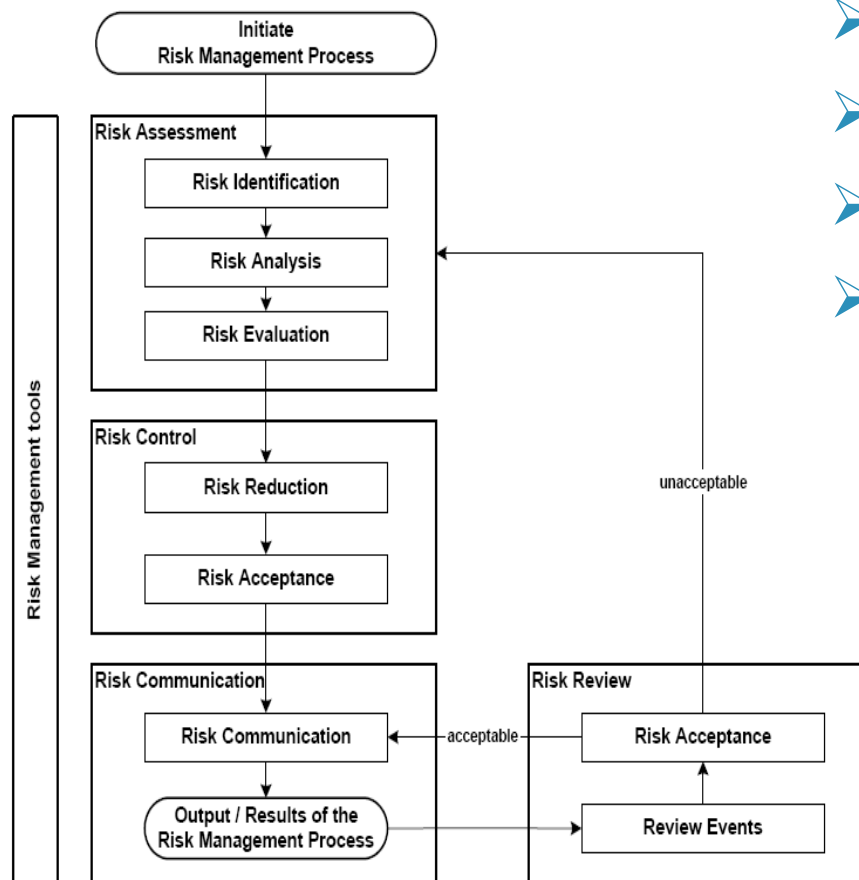
**U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)**

**June 2006
ICH**

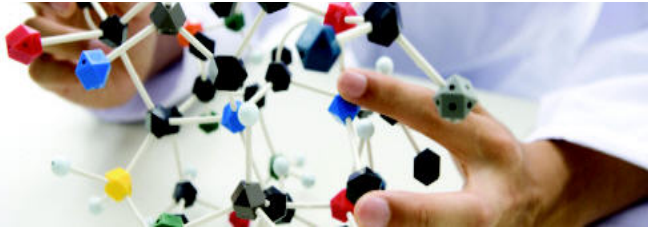


ICH Q9 QRM Process

Figure 1: Process flow of quality risk management

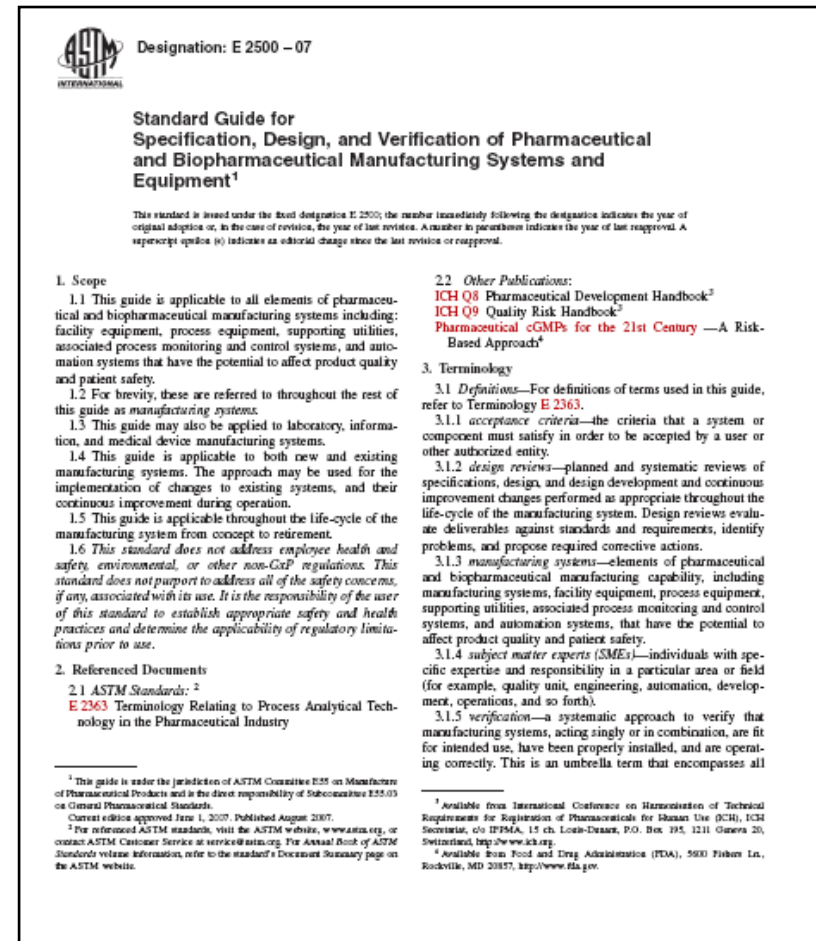


- Risk Assessment
- Risk Control
- Risk Communication
- Risk Review



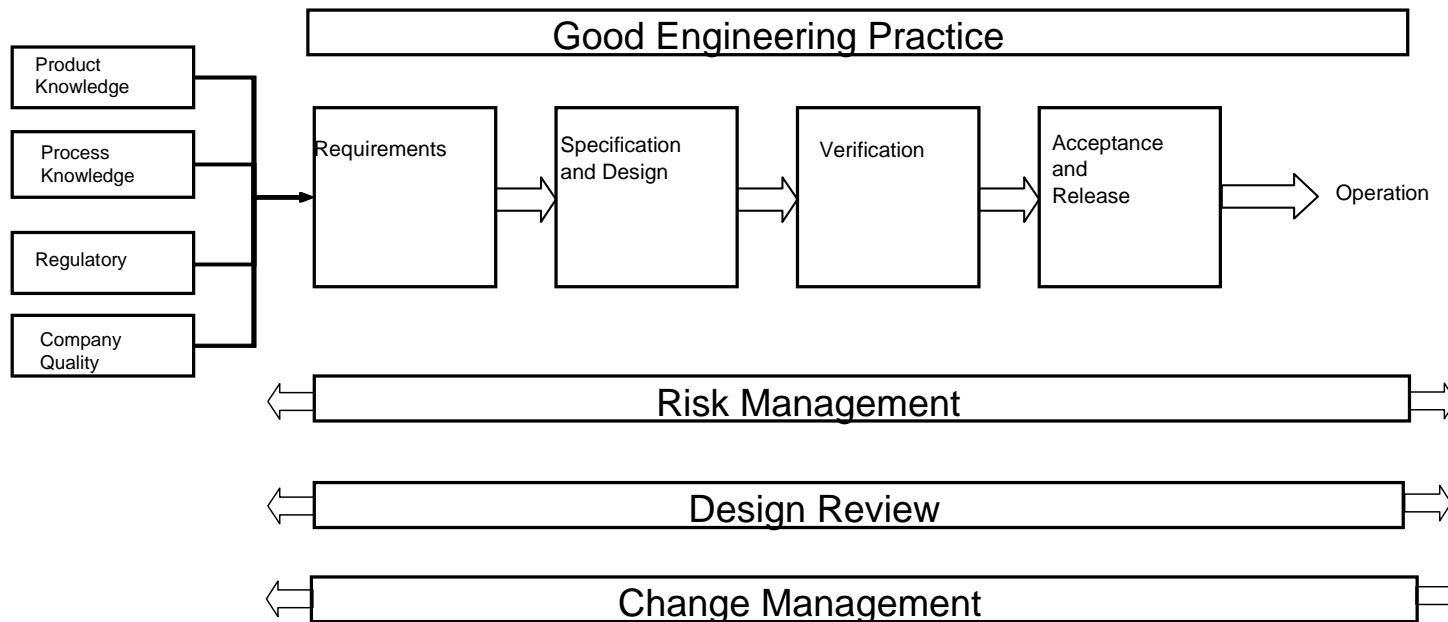
ASTM E-2500-07 Key Concepts

- Risk-based Approach
- Science-based Approach
- Critical Aspects of Manufacturing Systems
- Quality by Design
- Good Engineering Practice (GEP)
- Subject Matter Expert
- Use of Vendor Documentation
- Continuous Process Improvement

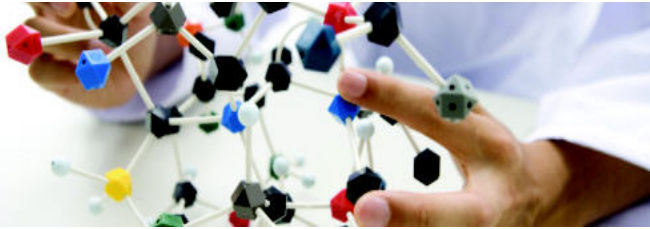




ASTM E-2500-07 – Applied Quality Risk Management

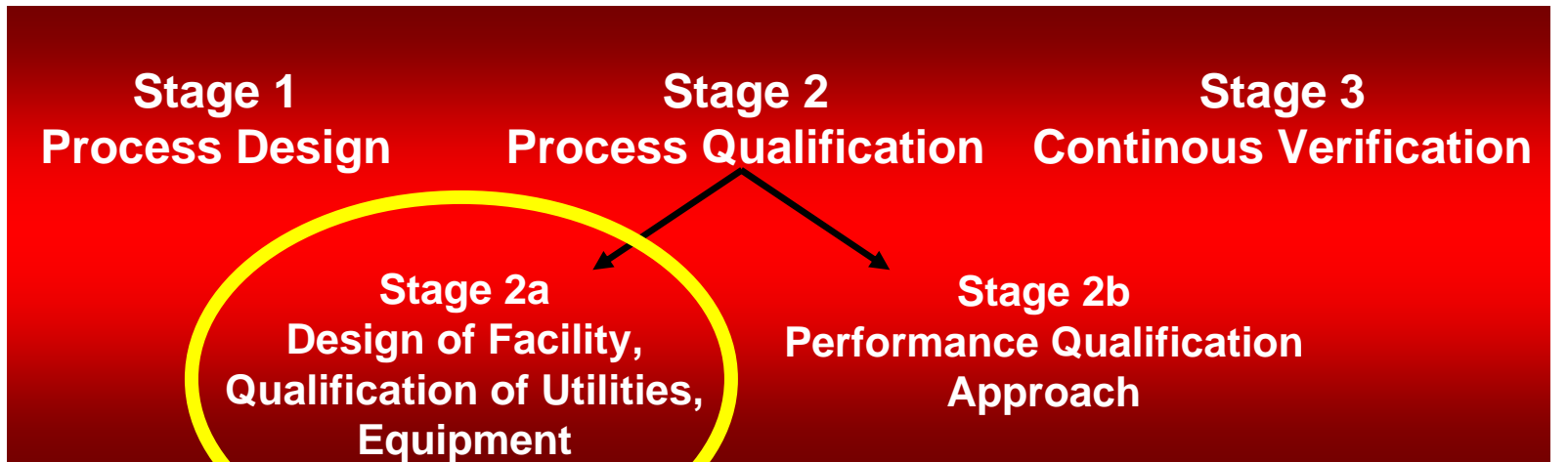


- Based on Principles of ICH Q9
- “Verification” as Umbrella Term Covering Both C&Q
- Traditional IQ and OQ Completely Absent



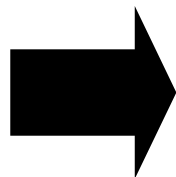
FDA Process Validation Guideline – How it Fits

ICH Q8 →
ICH Q9 →
ICH Q10 →



FDA Process Validation – General Principles and Practices

**ASTM
E-2500**



ISPE ASTM E-2500 Implementation Guide (DRAFT)

ISPE Good Practice Guide – Applied QRM in C&Q (DRAFT)

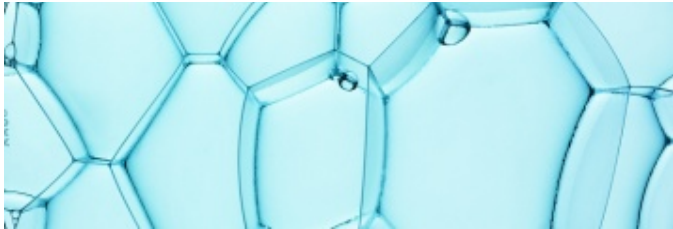
Slide Concept – Thanks to Dr. Christopher Smalley, Merck Co. , BioSterile Validation

Linking C&Q to Process Validation

Interphex NY 2011

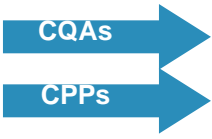
 **Abbott**
A Promise for Life

© 2011 Abbott www.abbottcontractmfg.com



Facility and System Design in the Big Picture

Process Knowledge Design Space



STEP	FUNCTION	FAILURE MODE	POTENTIAL EFFECT OF FAILURE	CAUSE OF FAILURE	O	S	D	RPN
1.0	Injection molding							
1.1	Transfer of molded components to inspection sites	Bacterial endotoxin cross-contamination of molded components during transfer to inspection sites	Bacterial endotoxin cross-contamination of molded components	Bacterial endotoxin transferred from equipment surfaces	1	3	3	9
1.2	Inspection sites	Manual handling of molded components	Bacterial endotoxin cross-contamination of molded components	Operator personnel cleanliness level hands	1	3	3	9
1.3	Packaging	Manual handling of packaged molded components	Bacterial endotoxin cross-contamination of molded components	Operator personnel cleanliness level hands	1	3	3	9
1.4	Transfer and storage	Bacterial endotoxin contamination on the surface of packaging from plant and transport	Bacterial endotoxin cross-contamination of molded components	Water from plant environment	1	1	2	2
2.0								
2.1	Plastic tubing extrusion							
2.2	etc.							

Process Risk Assessment

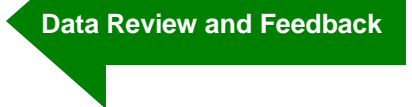


Identify Requirements



Continuous Improvement

Build



Commercial Operations



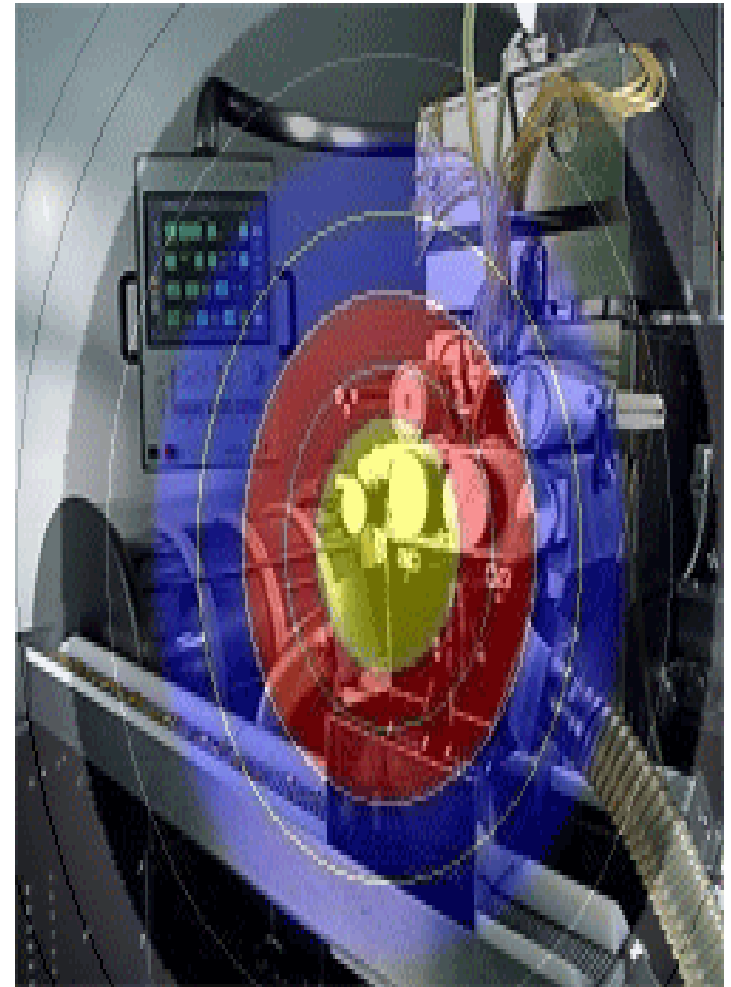
Ongoing Quality Data Monitoring

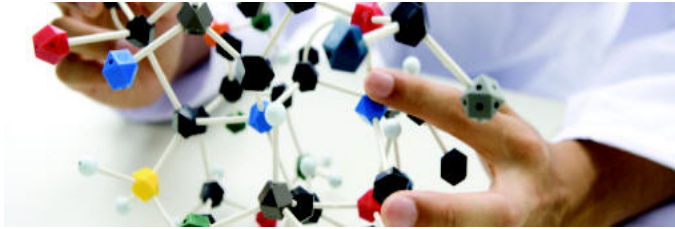
Linking C&Q to Process Validation
Interphex NY 2011



Implications for Facility and System Design

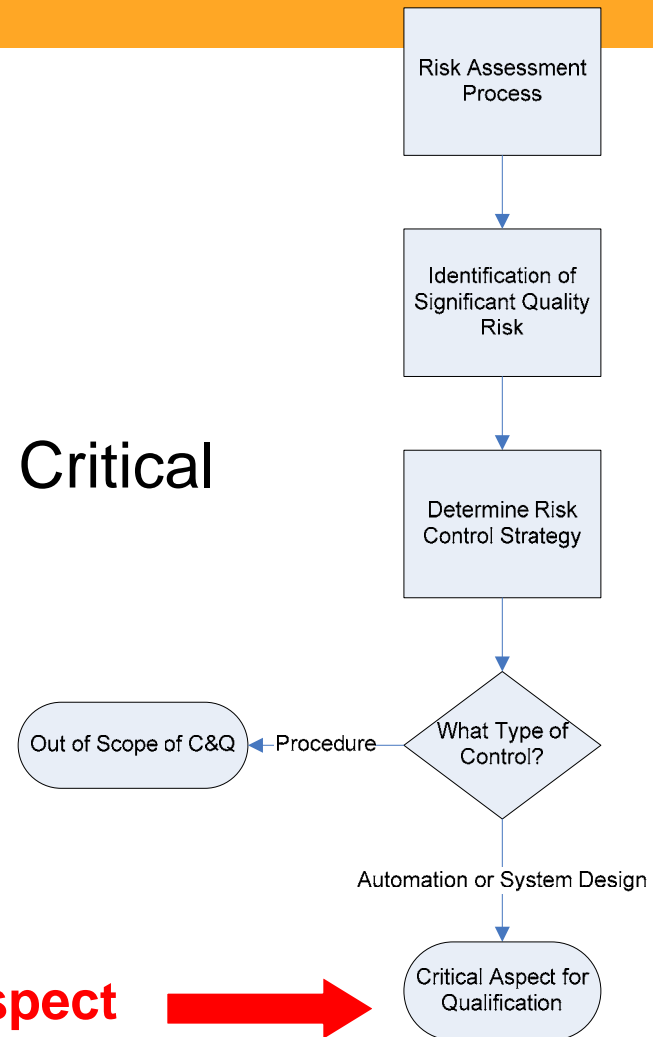
- “Fitness for Intended Use” requires defining specific process requirements
- Can’t assume off-shelf-system meets process requirements – evaluate & document
- Identification of “Critical Aspects” is key
- Focus of QA-approved Qualification and change control on Critical Aspects
- Performance / maintenance of Critical Aspects focus of rest of lifecycle (periodic review, critical PMs, calibrations, etc.)





Identification of Critical Aspects

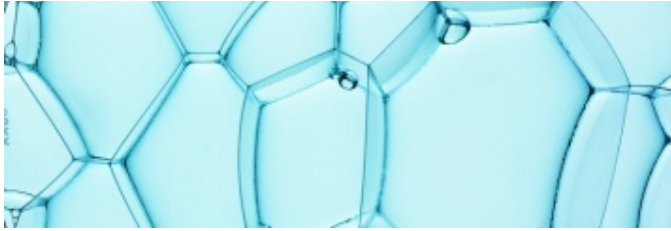
- Identify Risk
- Identify Control Measure
- If Control is Design Feature = Critical Aspect



Critical Aspect



Critical Aspect for Qualification



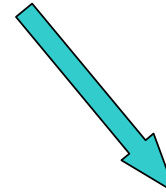
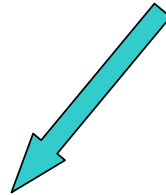
Process Risk Assessments and Manufacturing Risk Assessments

Product / Process Knowledge



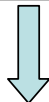
Product Process Risk Assessment

Same Everywhere Process is Run



Typical Project Team Responsibility

Design Risk Assessment Site A



Critical Aspects List – Site A

Site specific manufacturing conditions

Design Risk Assessment Site B



Critical Aspects List – Site B



Transitioning from Legacy Practices

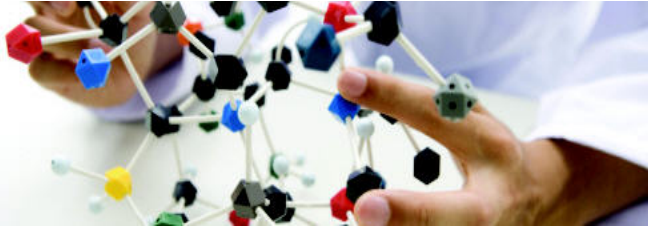
- Firms just starting out can establish completely ICH Q9 / ASTM-E-2500-based C&Q procedures and practices
- Established firms may need to develop bridging strategies to get from here to there



Linking C&Q to Process Validation

Interphex NY 2011





Span of the Bridge



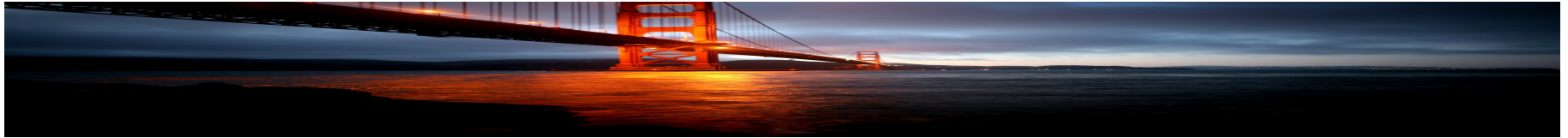
Organizations need to determine “how far along the bridge” they go
Cost, time, organizational maturity, culture/regulations are all factors

The only things not “flexible” are the program's objectives:

- Systems meet process requirements
- Risks to patients are adequately controlled
- Documented evidence of fitness for intended use is available



Ends of the Bridge

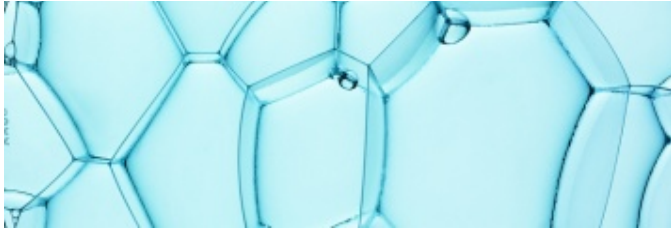


Traditional Qualification

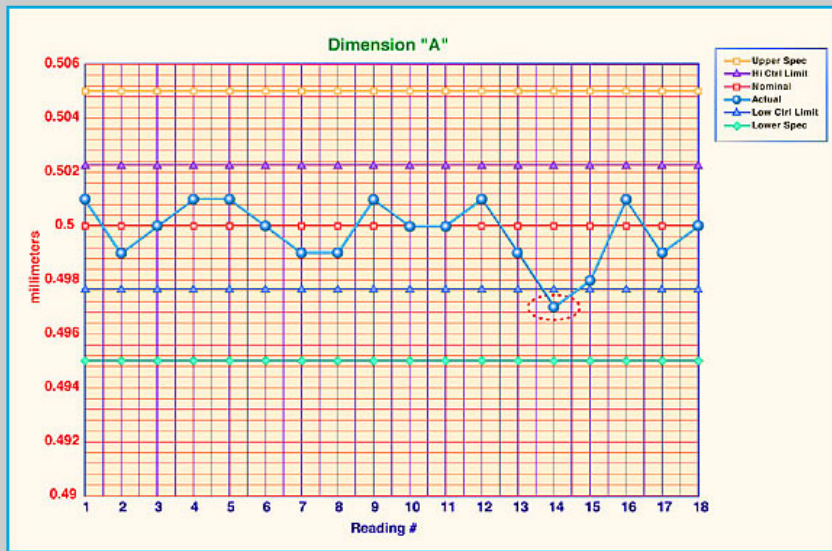
- Specification and design separate from “Qualification”
- Asset-based approach
- IQ/OQ testing as source of evidence
- Qualify all systems
- Emphasis on documents
- Want “Pretty” documents
- No “deviations”
- Primary objective: Perception of regulatory compliance

ASTM E 2500 Verification

- Requirements/specification/ Design/Build/Test – all one process
- Product process-based approach
- Commissioning is primary evidence source
- Emphasis on performance
- Documentation w/ technical merit
- Only Quality-Critical nonconformances relevant
- Primary Objective: Patient protection through Quality Risk Management (QRM)



Maintaining a “Qualified State”



- “Qualified State” = State of control with risks to product quality adequately addressed
- Use of statistics by Process Validation guideline is not new – but emphasis is
- Expect to be asked for statistical measures of performance where applicable
- Be aware of the “story” your data tells



Lifecycle Approach – Not Just for Products

System Lifecycle Elements =

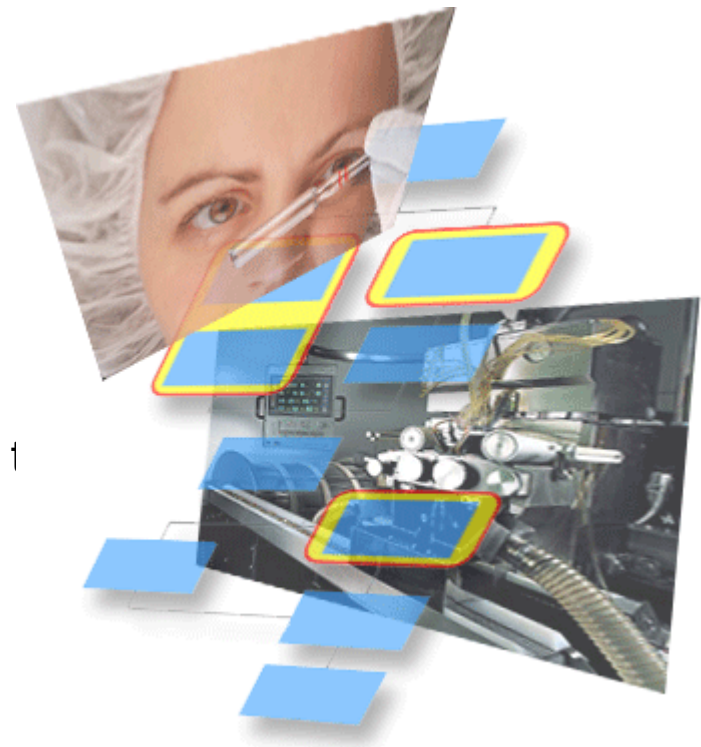
- Change Control
- Change Control
- Change Control
- CPPs Recorded
- Data Trended (as applicable)
- Exceptions and Investigations
- Periodic Review
- Calibration Program
- PM Program
- Always - GEP



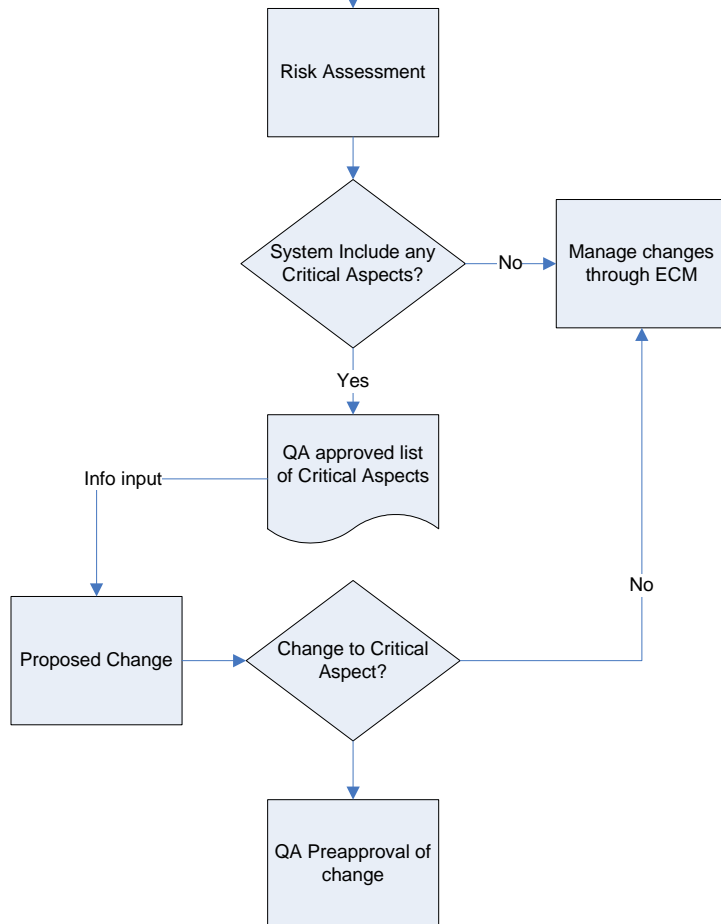
Change Control According to Risk

- Indirect and No Impact Systems – *Engineering Change Management*
- Direct Impact Systems – *Operational Change Management*
 - “...all changes require prior approval by the Quality Unit, unless predefined arrangements are established covering specific types of changes ...”
 - “...all changes should be communicated to the Quality Unit.”

ASTM E 2500 07



Operational Change Control



Possible “Predefined Arrangements”...

- Systems w/o critical aspects (“Indirect” or “No Impact”) under ECM
- Changes to non-critical aspects under ECM
- Need documented and QA approved critical aspects list for each system
- Need to address “shop floor” application

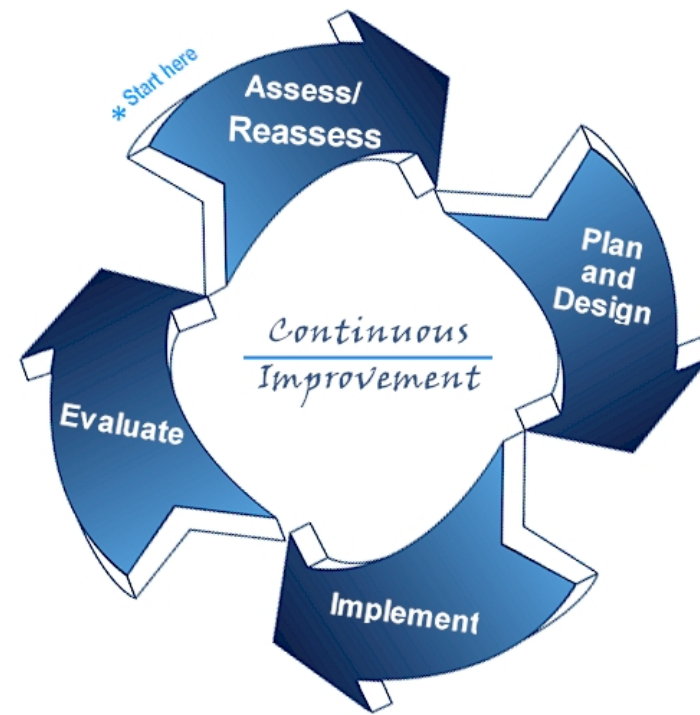


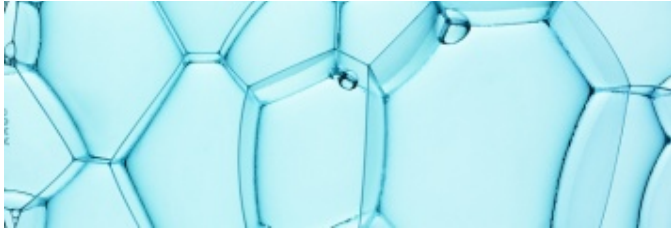
Change Control and Continuous Improvement

Efficient change management is a key to continuous improvement

“Change management should provide a dependable mechanism for prompt implementation of technically sound improvements following the approach to specification, design, and verification described in this document.”

ASTM E 2500 07





Calibration Requirements

System instrument calibration requirements

Based on risk

- Accuracy ratios
- Exception docs for out-of-tolerance
- Calibration intervals

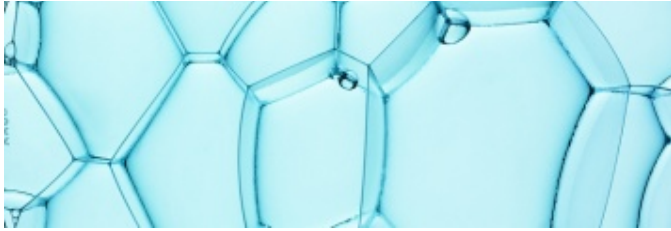


Linking C&Q to Process Validation

Interphex NY 2011

 **Abbott**
A Promise for Life

© 2011 Abbott www.abbottcontractmfg.com



Preventative Maintenance

Critical Maintenance

- Critical PM's may NOT be based on system's functional criticality
- Example: PM for replacement of a gasket may be critical if failure to replace will result in extraneous matter in product
- Criticality of PM should be tied to risk to product quality if PM not performed or not performed on time

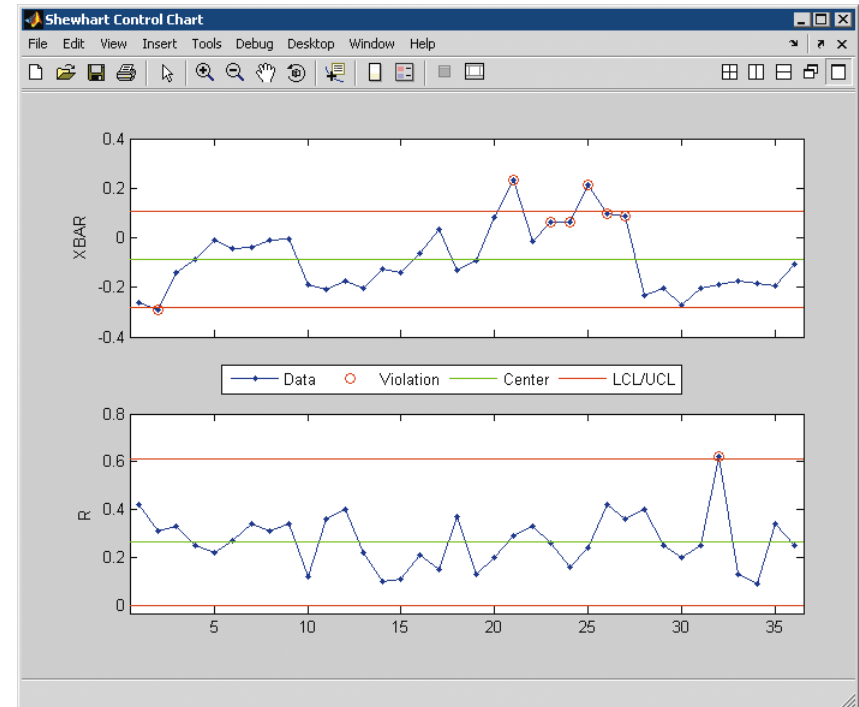


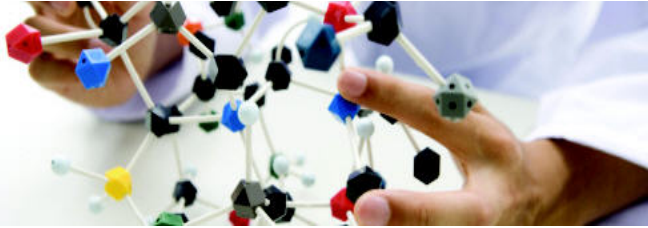


Periodic Review

Review & Requalification

- ASTM silent
- Reasonable to apply Q9 risk management principles
- Are you monitoring and recording critical parameters?
- Does routine process data assure system performance is in state of control?
- Would change in performance be detectable?





Legacy Systems

Strategies for Dealing with Legacy Systems

As a “Project” or “Initiative”



On an “As-They-Come-Up” basis

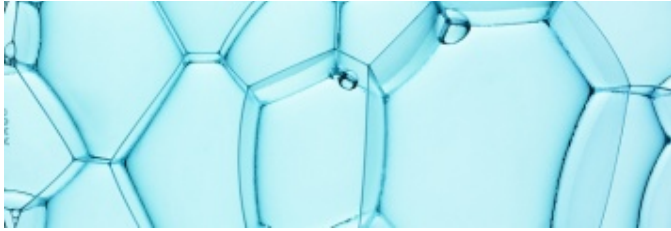




Risk Evaluation Project

- Prioritize current VMP inventory
- Determine cost/benefit on each item
- Assign resources and plan
- Execute plan for evaluations





Evaluate as Changed

- Status quo until item/process modified
- When change proposed, decision is made on additional evaluation
- Opportunity may be for engineering team responsible for change to drive risk evaluations





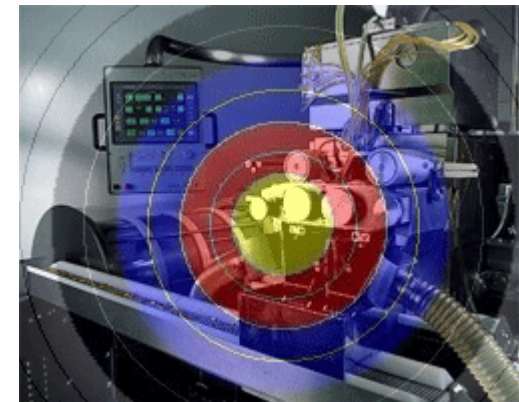
Understanding Legacy System Quality Impact

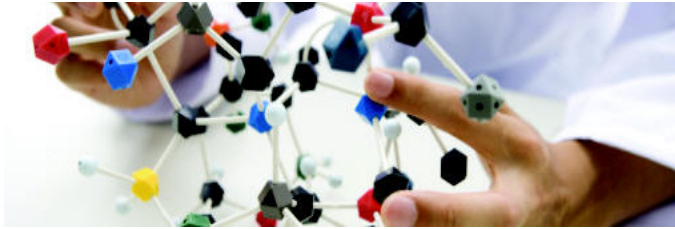
Keys to Evaluation of a Legacy System

- Understanding of process requirements it supports (CQAs, CPPs, etc.)
- Understanding of designed Control Strategies (Functional Specs.)
- Understanding of what it actually has been doing (Quality History)

In the likely absence of formal Process Requirements, such requirements can be reconstructed from manufacturing batch records, SOPs, development reports, etc.

Vendor manuals, SOPs, engineering drawings may provide ability to reconstruct “Functional Specs”





Evaluation Pros and Cons



Pros

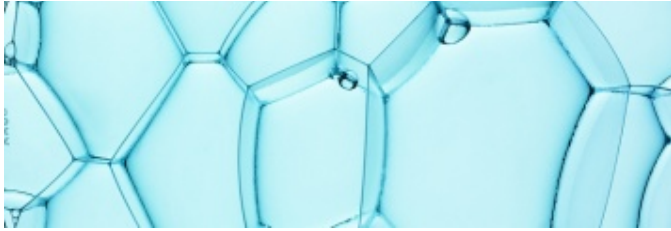
- Potential to Reduce Qualified Inventory
- Streamline Change Control
- Reduce Periodic Reviews
- Focus Resources and Time



Cons

- Takes Time and Resources
- Can Complicate Change Control
- Need to be Ready for the Answers!





Some Lessons Learned

- Implementation at sites needs to be top-down – management must be obviously in support
- QA acceptance is a bigger hurdle than Engineering willingness
- Expectations for documentation must be communicated to – and agreed by – vendors/suppliers
- Quality unit review of commissioning documents has been one of our biggest challenges





Industry Needs Going Forward

- Regulators who walk-the-talk on risk based approaches
- Industry that understands the opportunities and responsibilities – not simply viewing RBA's as chance to “do more with less”
- Continued leadership from key industry groups and participation of “big pharma” in an evolutionary process
- QA units that understand that more is not necessarily better
- Good Engineering Practices – and Good Engineers





Building Blocks to Tie C&Q to Process Validation



- Process Knowledge is key
- Evaluate manufacturing risks to product
- Identify controls and control strategies incorporated in design
- Risk controls = Critical Aspects = Qualified
- Qualification = State of Documentation and Control
- Lifecycle - Not Event
- Continuous review and improvement based on Quality data – listen to the “voice of the process”



Questions or Comments?



David Dolgin
Senior Quality Program Manager
Global Quality Systems
Abbott
Global Pharmaceutical Operations

dave.dolgin@abbott.com