



## Presentation Overview



- Overview of Risk Assessment Guidance Documents
- Case Study Examples
- Project Takeaways / Lessons Learned

## In the Beginning.....

- There were no Risk Assessments
- All Equipment was Qualified
- Same Level of Effort for:
  - AHU's and Air Compressors as WFI Loops and Process Vessels
- Excessive resources required for validation projects.



## ISPE Baseline Guide 5



- Standardized Risk Assessment Approach Using Impact to Product Quality
  - System Level Impact Assessment
  - Component Criticality Assessment
- Focused Resources on what was Critical
- No more qualifying Air Handling Units



## ISPE Baseline Guide 5

- Introduces the Concept of Integrated C&Q
  - Commission Indirect Impact and Direct Impact Systems
  - Leverage Commissioning Work into Qualification
- Goal to Eliminate Redundant Testing
- Reduce Qualification Resources and Expedite Timeline



## ICH Q8/Q9/Q10

- High Level Guidance Documents
- Intended for the entire drug product lifecycle
  - Development → Discontinuation
- Provide Synergy between Regulatory Bodies
- Using Science Based Risk Assessments
- Overall Goal of Increasing Product Quality and Patient Safety



## ICH Q8 – Pharmaceutical Development

- Guidelines for Risk and Science based development of Pharmaceutical Product
- Introduces the Concept of Quality by Design
- Details Basic Elements of Pharmaceutical Development Program



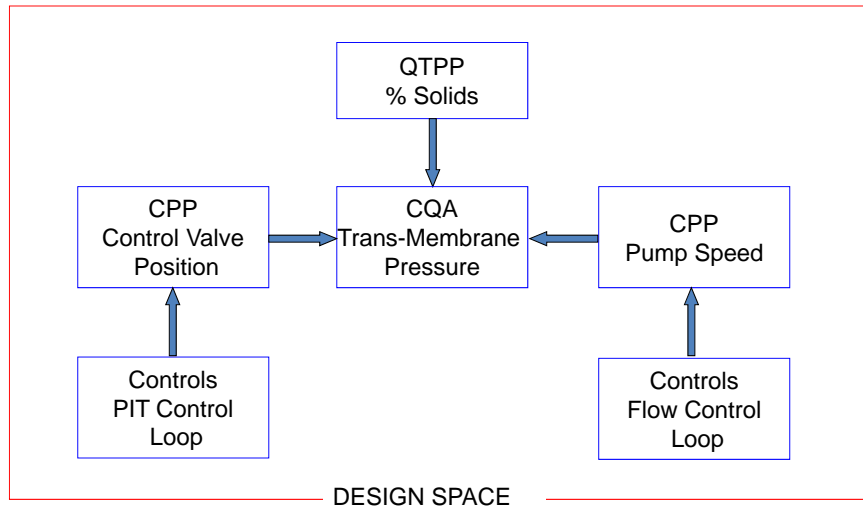
## ICH Q8 – Pharmaceutical Development Elements

- Quality Target Product Profile
- Critical Quality Attributes
- Risk Assessment Linking CQA's to CPP's
- Develop a Controls Strategy
- Develop the Design Space
- Product Lifecycle Management and Continuous Improvement

## ICH Q8 Elements - Example



UF/DF Final Concentration



## ICH Q9 – Quality Risk Management



- Guidelines for Managing Quality Risks throughout a Product's Lifecycle
- Two Key Tenets to Quality Risk Management

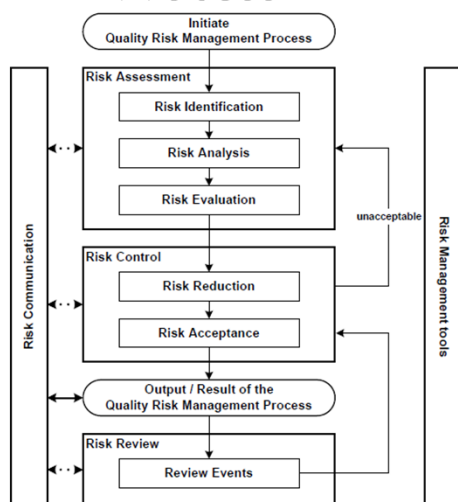
Based on Scientific Knowledge to Ultimately Protect the Patient

Level of Effort of should be commensurate with the Level of Risk

## ICH Q9 – Quality Risk Management Process

- Risk Assessment
  - Risk Identification, Analysis, Evaluation
- Risk Control
  - Risk Reduction, Acceptance
- Risk Communication
- Risk Review

## ICH Q9 – Quality Risk Management Process



ICH Q9 – 09Nov2005



## ICH Q10 – Pharmaceutical Quality Systems

- Guidance for Total Quality Management System throughout Product Lifecycle
  - Development
  - Tech Transfer
  - Commercial Manufacturing
  - Product Discontinuation
- Three Main Goals:
  - Achieve Product Realization
  - Establish and Maintain a State of Control
  - Facilitate Continuous Improvement



## ICH Q10 – Pharmaceutical Quality System

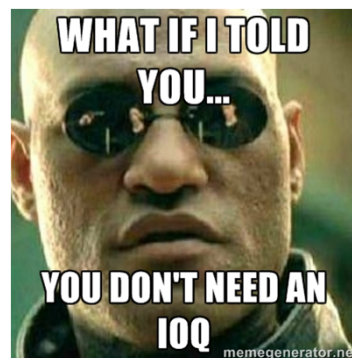
- Key Elements
  - Process Performance and Product Quality Monitoring System
  - Corrective / Preventive Action System (CAPA)
  - Change Management
  - Management Review of Process Performance and Product Quality
- Enablers
  - Knowledge Management
  - Quality Risk Management

## ASTM E2500

- Concise Guidance Document Structured on the following Concepts:
  - Risk and Science Based Approach
  - Critical Aspects of Manufacturing Process
  - Quality by Design
  - Good Engineering Practices
  - Use of Subject Matter Experts
  - Use of Vendor Documentation
  - Continuous Process Improvement

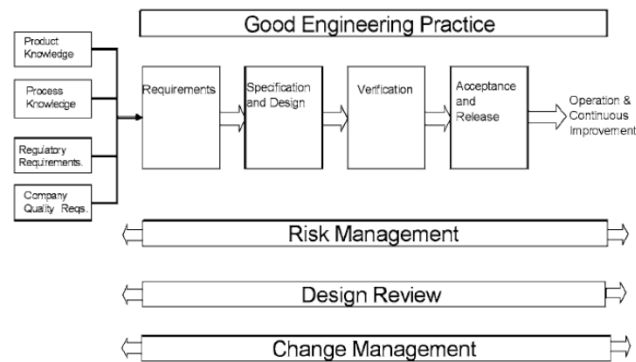
## ASTM E2500 Methodology

- Requirements Definition
  - Basis of Design and Verification
- Specification and Design
  - Translates the Requirements into a Functional Design
  - Critical Aspects of Process Defined and Documented
- Verification
  - Defined Acceptance Criteria
  - Verification Strategy
  - Verification Activities
  - Verification Review
- Acceptance and Release





# ASTM E2500



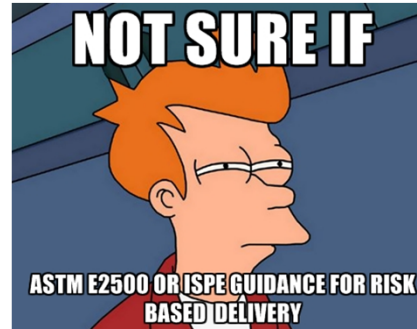
ASTM E-2500 -07 (2012)

## ISPE – Guidance to Risk Based Delivery of Facilities, Systems and Equipment

- Expanded on ASTM E2500 Focusing on the following Concepts
  - Science Based Quality Risk Management
  - Product and Process Understanding
  - Flexible Approach to Specification and Verification
  - Achieving Fitness for Intended Use
  - Clarification of Roles and Responsibilities
  - Leveraging Supplier Activities

## ISPE Guidance

- Verification Achieved Similar to ASTM E2500
  - Define Critical Aspects of the System (CQAs, CPPs)
  - Define a Verification Strategy
    - Define Acceptance Criteria
    - Verification Activities
    - Verification Review
  - Acceptance and Release
    - Fit for Intended Use



## Case Study

- Multi-Phased Project for Commercial Expansion



## Case Study

- Phase 1 – Quality Control Laboratory
  - Associated Utilities – HVAC, Compressed Air
  - Autoclaves, Refrigerators, Stability Chambers, Glassware Washers
- Approximately 20 Different Systems
- Phase 1 Project Duration approximately 1 year (2005-2006)



## Case Study – Phase 1

- Phase 1 – Traditional Validation
  - No Risk Assessments Performed
  - No Commissioning
- All Equipment IQ/OQ/PQ
  - Release for Use after PQ Final Reports
- Unnecessary Efforts spent Qualifying AHU's and Air Compressors
  - Now Stuck with Re-Validation for any System Changes

## Case Study

- Phase 2 - Bulk Manufacturing Suite and Powder Filling Suites
  - Process Air, WFI, Clean Steam, HVAC
  - Process Vessels, TFF, Lyophilizers, Fill/Pack Lines
- Approximately 100 Different Systems
- Project Duration of under 2 Years (2007-2009)

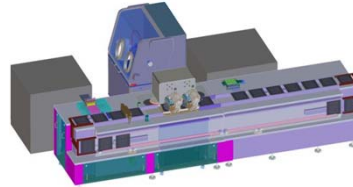


## Case Study – Phase 2

- Implemented an Integrated C&Q approach using ISPE Baseline Guide 5
- System Boundaries drawn on all P&ID's
- System Impact Assessments performed for all systems
- CCA's for all Direct Impact Systems
- Commissioning for Indirect Impact and Direct Impact Systems
- Qualification for Direct Impact Systems

## Case Study

- Phase 3 – Additional Filling Suites
  - Filling and Packaging Equipment, Washers
  - HVAC
- Approximately 20 Different Systems
- Project Duration Scheduled for 6 months.
  - Project ongoing – Scheduled Completion 12/14



## Case Study

- Phase 3 – Implementing ASTM E-2500 Approach
  - Detailed Requirements Specification
  - Defined Critical Aspects of Filling and Packaging Process (CQAs / CPPs)
  - Defined Verification Activities as part of Verification Plan
  - Using Vendor Documentation (FAT / SAT) as part of Verification Package.

# Case Study



Installation Verification			
Required Element	Associated Task	FAT	IV
Drawing Verification	Complete drawing walk-downs, including PFDs, machine diagrams, electrical and pneumatic schematics to verify they are complete, accurate and reflect the As-Built status.	Verify current revision of dwgs (redlines are acceptable)	Verify that redlines documented during the FATs have been converted to final CAD.
Critical Component Verification	Documentation of the quality attributes for critical components, e.g., Model, Tag/Label, Manufacturer, are installed correctly in field, per specification/drawings.	Verify installation of all critical and non-critical components	Verify only those critical components that were changed/ modified or installed after FAT
ETOP	Confirm ETOP is approved and binder includes all relevant procurement documents, design specifications, design drawings, submittals & supplier documentation, O&M manuals, Spare Parts List, etc and that they are complete and stored on file in QA archive.	N/A	Verify contents of ETOP
Utilities Verification	Verify that the support utilities associated with the equipment modifications (e.g., Compressed Air and Electrical Supply) are connected in accordance with the specifications and that all physical installation requirements have been met.	Verify vendor supplied utility systems (i.e. voltage, frequency, pressure, etc.)	Verify installation of critical utility services at site
Instrument Calibration	Verify that all critical instruments requiring calibration are within current calibration and included in the calibration program; and that the documentation is NIST or other applicable traceable standards.	Document Factory Calibration at final FAT	Verify calibrations performed by MKC are current for each instrument/equipment
Input/Output Verification	Verify that each of the Control System I/O is properly identified and installed as per manufacturer and MannKind's specifications.	All critical I/O will be verified in accordance with internal SOP	Verify Representative sampling; percentage or specific critical I/O.
Software/Hardware Verification	Verify the installation of the operating/control of the equipment and HMI interface software associated with the equipment and Vision Systems.	Verify the current version of the software application/ program with each version of FAT	Verify final version of software application/ program

# Case Study



Operational Verification			
Required Element	Associated Task	FAT	OV
Instruments, Indicators, and Controls	Functionally test all critical to product quality instruments, indicators, and control devices.	Verify	Verify representative sampling based on critical to product quality.
Interlocks and Safety Devices	Test and verify proper operation of all product and/or process critical safety device hardware and mechanical / electrical interlocks	Verify	Refer to FAT Attachment/test script
Alarms/Interlocks	Verify critical alarm conditions that impact product or process quality along with the associated interlocks.	Verify	Verify representative sampling based on critical to product quality;
Configuration Settings	Verify all critical configurable system and/or device settings (configurable devices may include VFDs, FFB devices, hardware, HMI etc.) for all equipment/ systems.	Document at final FAT	Verify only those settings that were modified or changed after FAT execution
Screen Navigation	Verify system screens are accessible and navigation touch buttons operate as specified (e.g. submenus, etc.)	Verify at final FAT	Verify only those settings that were modified or changed after FAT execution
System Security	Verify all security measures (physical, procedural, or logical) identified for the system, including HMI controlled access to screens/ functions, as applicable.	Verify at final FAT	Verify representative sampling based upon user group and level of access, e.g. operator /supervisor/maintenance
Machine Capability	Verify each critical operating range is controlled within acceptable limits when a valid set-point is configured for the system, e. g. speeds.	Document at final FAT	Verify only those settings that were modified or changed after execution of final FAT
Sequence of Operations	Test the design Sequence of Operations to verify proper operation and sequencing of control operations, as appropriate.	Verify	Verify
Power Loss and Recovery	Perform Loss of Power testing to confirm the equipment can be safely re-started (or automatically restarted) and that setpoints and configurable parameters are not lost or altered by the loss of power.	Verify	Verify

## Project Takeaways – Phase 1



- Traditional Validation Approach
- Would have benefitted from a Risk-Based Integrated C&Q Approach
  - Systems unnecessarily qualified
  - Could have leveraged FAT Testing
  - Resources spent resolving deviations in Qualification that could have been more easily addressed in Commissioning

## Project Takeaways – Phase 2



- System Impact Assessments Eliminated Unnecessary Qualifications
  - No AHU's, Air Compressors, etc.
- Involve Quality earlier on in Commissioning Activities
  - Not all Commissioning was able to be leveraged into Qualification
  - Resulted in Performing some verifications twice



## Project Takeaways – Phase 3

- Quality Involved Early on (Became SME)
- Knowledge Learned from Phase 2 allowed for definition of critical aspects early on.
- Clearly Defined what FAT/SAT Verifications would be part of Qualification Package
- Reduced Overall Qualification Time



## Summary

- ISPE Baseline Guide 5 Still a Popular Option
  - Straightforward Approach to Risk Assessment
  - Powerful Tool to Tailor Qualification Activities
  - Beneficial For Younger Companies or when there is Limited Process Experience
  - Useful for larger projects with many systems
- Doesn't truly capture Critical Quality Attribute
  - Only Components related to them





## Summary

- ASTM E2500 Dramatically Different Approach
  - Requires SME's and extensive process knowledge
  - Define what is important up front
  - Verify what is important for product quality
  - Eliminates unnecessary qualification testing



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