Boston Chapter
March 21, 2013

Introduction to ISPE GUIDE:

SCIENCE AND RISK-BASED APPROACH FOR THE DELIVERY OF FACILITIES, SYSTEMS, AND EQUIPMENT

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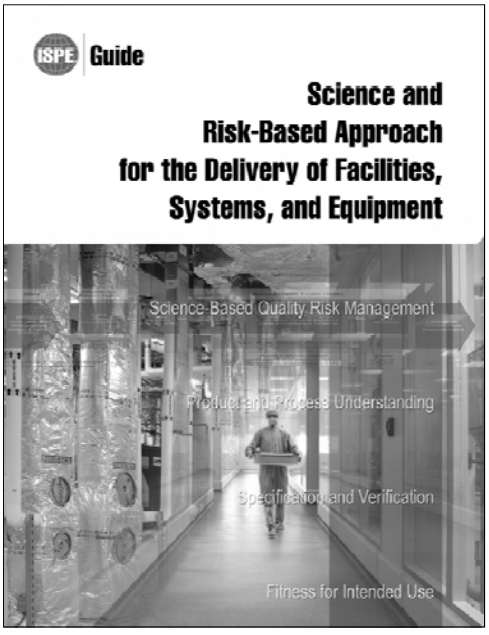
Connecting a World of Pharmaceutical Knowledge



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Agenda

- Why a Risk Based Approach?
- Introduction and Overview of ISPE GUIDE: *Science and Risk-Based Approach for the Delivery of Facility Systems and Equipment (FSE)*
- Guide Content

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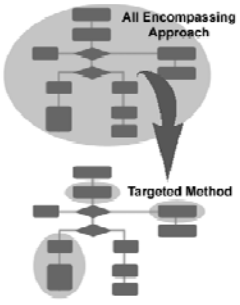
What is a Science and Risk Based Approach (RBA)?

A paradigm shift is occurring in the global pharmaceutical industry. The pharmaceutical industry, in conjunction with ISPE is applying an all-encompassing approach to qualification and toward using focused methodologies to assess the scope of qualification.

A science and risk based approach to Qualification of applicable systems and facilities consists of:

- The identification and control of risks to product quality
- Formality and documentation commensurate with risk
- The use of Good Engineering Practices (GEP) to verify installation and operation of systems
- Verification that system performance meets product and process user requirements



Think about it:
If everything is critical, then nothing is.

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Qualification – A Broken Process

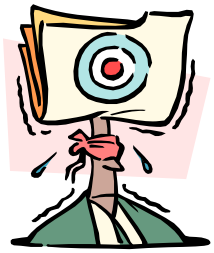
IQ/OQ had become more intensive than PQ.

Organizations refused to leverage commissioning

Automated systems and the controlled equipment were qualified separately and inefficiently

Deviations for trivial items diluted Q-unit attention

"Change-is-bad" attitudes driven by cost/time



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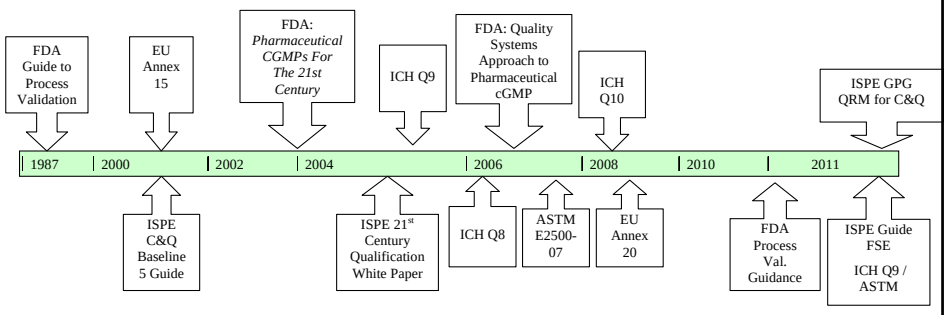
Evolution Of Commissioning & Qualification



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In the Beginning…

A number of seminal documents established the principles of a RBA:

- ISPE Baseline Guide 5 (2001)
- "Pharmaceutical cGMPs for the 21st Century – A Risk Based Approach" – FDA (2004)
- ICH Q8 Pharmaceutical Development Handbook (2008)
- ICH Q9 Quality Risk Handbook (2006)
- ISPE White Paper – "Risk Based Qualification for the 21st Century" (2005)
- ASTM E 2500 (2007)

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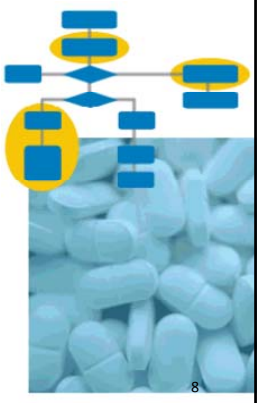
10 Principles for Risk-Based Qualification

1. Focus on that which affects product quality
2. Process User Requirements key to acceptability (IQ/OQ subordinate to PQ)
3. Risk assessments and process knowledge used to identify critical elements
4. Only critical features/functions to be qualified
5. All activities must contribute value
6. Risk-based asset delivery – not "cookbook" requirements
7. Value-added documents based on technical merit
8. Use of supplier documentation
9. Test planning (and one-time testing)
10. Foster innovation – all change is not bad

ISPE White Paper "Risk Based Qualification for the 21st Century" March 2005



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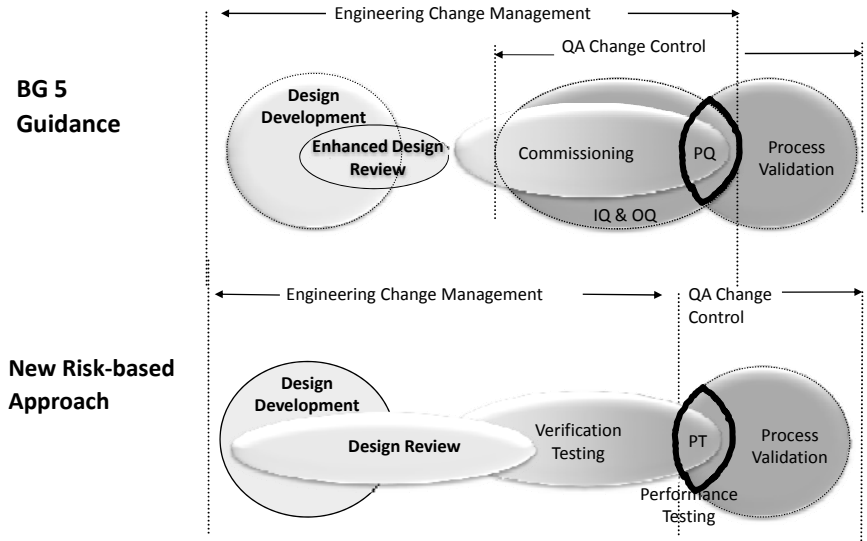
Scope of BG 5 vs. FSE GUIDE



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Verification ~~vs.~~ as Qualification

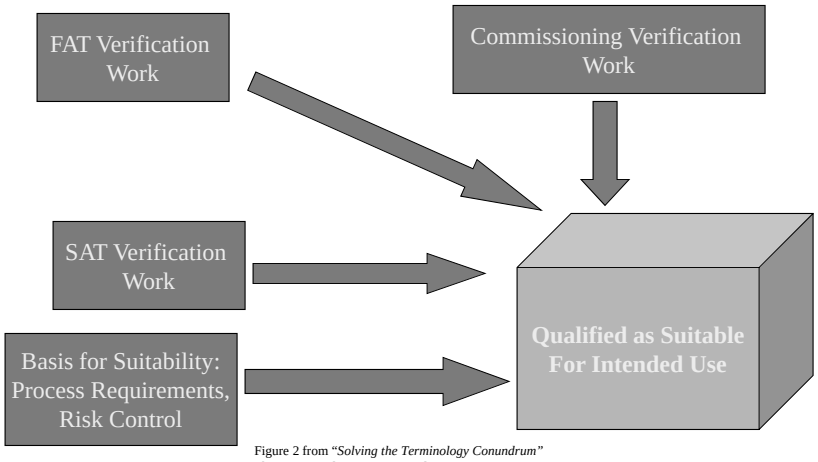

Figure 2 from "*Solving the Terminology Conundrum*" Pharmaceutical Engineering, July/August 2008

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Qualification -"Traditional" vs. RBA

Traditional Approach

(Product) User Requirements not Formally Documented

Protocols Developed from "Templates"

IQ/OQ Protocols "Preapproved"

Commissioning not Leveraged

Engineering and "Validation" Personnel Often Distinct

Emphasis on Documents – Not System Performance

RBA Based on ASTM E 2500

Process Requirements Documented, Approved

Risk Assessments Determine Critical Aspects of Design

Engineering Testing ("Commissioning") Verification

All Documents with Technical Merit Used as Evidence of Fitness for Use

Emphasis on Meeting Process Requirements

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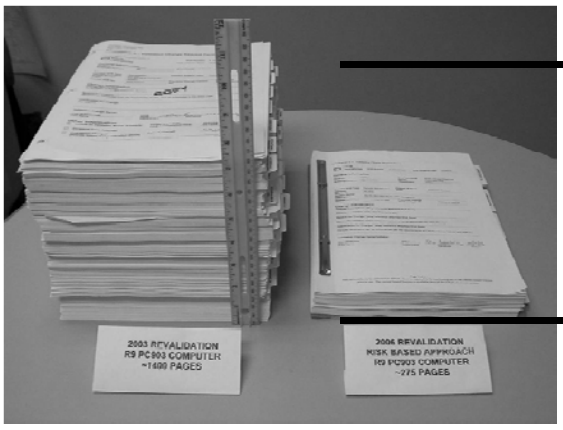
Eyes on the Prize



= **Time & $$$ to Focus on Critical Quality Issues**

Actual photo of an Abbott Laboratories risk based revalidation paperwork for a legacy control system (on right) vs. previous revalidation "testing everything"

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FSE- Rationale for the New ISPE GUIDE

Presents a structured lifecycle approach to the delivery of facilities, systems and equipment which support these regulatory initiatives

Designed to improve the way in which the industry delivers regulated manufacturing capacity

- Improve the ability to meet documented process requirements
- Control risks within the manufacturing process
- Produce high quality products which consistently meet product user requirements.

The GUIDE describes the *Principles* required when applying a science and risk based program.

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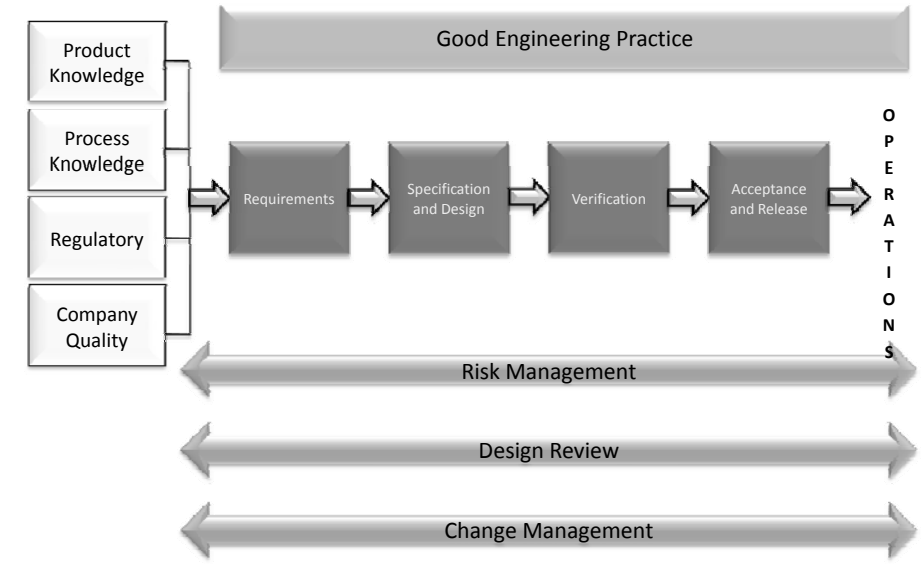
Structure of FSE GUIDE



Reference: Figure 1: ASTM E2500-07, pg 3

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FSE GUIDE Overview

Chapters Titles

1	Introduction
2	Overview Of The Lifecycle
3	Requirements
4	Specification & Design
5	Verification, Acceptance and Release
6	Continual Improvement
7	Quality Risk Management
8	Good Engineering Practice
9	Design Review
10	Change Management
11-15	Appendices
16	Appendix 6 Glossary and Acronyms
17	Appendix 7 References

Note : Automation dealt with throughout each chapter

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Introduction

This Guide is a key part of the validation life cycle approach to quality assurance to ensure the manufacture of safe and effective products.

The Guide is designed to improve the way in which industry delivers regulated manufacturing capacity:

- to documented process requirements
- control risks within the manufacturing process
- produce high quality products
- consistently meeting product and process requirements

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Background

- The successful delivery of manufacturing facilities (including small, large, new, expansion, or renovation type projects) regulated by various authorities, poses significant challenges to manufacturers, engineering professionals, and equipment suppliers.
- These facilities are required to meet all applicable GxP regulations, and to comply with all other relevant local and international governing codes, laws, and regulations.
- This Guide has been published in support of the principles provided in these publications and to provide specific implementation guidance on meeting the expectations of global regulators as embodied in the ICH documents, as applied to the design and delivery of regulated facilities

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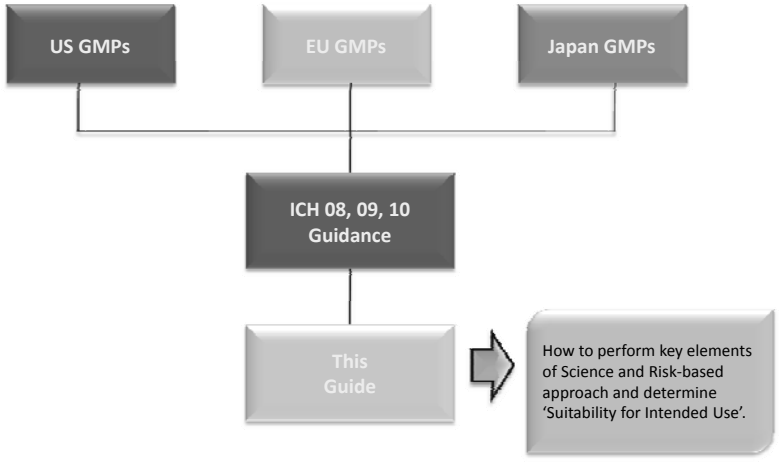
Relationship of this Guide to International GMP Regs and ICH Guidance Docs



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Scope

- Planning, specification, design, and delivery of facilities/utilities/equipment and associated automation (harmonized) *with GAMP 5*
- All pharmaceutical manufacturing
- Addresses the verification (or qualification) portion of the validation life cycle on which process validation is built
- New commercial manufacturing and modification to existing regulated mfg facilities

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Purpose

- Objective is to facilitate the translation of the scientific product and process knowledge into a documented specification, design, and verification of equipment/systems/utilities which are fit for intended use, and minimize risk to patient safety and product quality

- Approach is built on science based quality risk management, and concepts of Quality by Design

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Benefits

Encourage the industry and individual organizations to reassess the terminology, practices, and roles and responsibilities involved in delivering new manufacturing capacity to focus on the criteria required to establish suitability for intended use

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Key Concepts

Science Based Quality Risk Management

- Describes the importance of a QRM program
- Documented risk assessments focused on risk to patient
- Focus on identifying , assessing and controlling risk

Product and Process Understanding

- Resulting from scientific investigation
- Enhanced continually during ongoing operations
- Begins with knowing the product CQAs and associated CPPs (ICH Q8R2)

Focus on Achieving Fitness for Intended Use

- Verification activities focused on confirming that CAs of equipment/systems and associated meet acceptance criteria
- Verification inspections and tests are not limited to CAs

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Key Concepts (cont.)

Flexible Approaches to Specification and Verification

- Several approaches to structure the documents, inspections, and testing activities
- Demonstration of fit for intended use and sufficient to meet regulatory expectations

Clarification of Roles and Responsibilities

- The roles of Quality Unit and SME are described in the context of the scope of activities covered by this Guide. Subject Matter Experts (SMEs) are defined as those individuals with specific expertise in a particular area or field
- The Quality Unit has a key role within the quality management system governing facilities, systems, and equipment. In addition to acting as a Subject Matter Expert (SME), the Quality Unit is responsible for overseeing quality and compliance

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Role of the Quality Unit

A key focus of the Quality Unit is identifying and approving those aspects that are required to manufacture a quality product, and to ensure that appropriate procedures are followed to ensure that risks to the patient in the manufacturing systems are adequately controlled

The QRM approach recognizes that the GxP regulations provide the Quality Unit with the responsibility for ensuring controls to assure drug product quality

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Role of the Quality Unit

- The actual performance of activities that contribute to that assurance, e.g., determine of appropriate procedures and specifications, may be performed by other most qualified departments or units, so long as this is agreed by the Quality Unit and the final Quality Unit review is preserved in the design of the verification/validation program
- The Quality Unit is expected to identify, approve, and verify those aspects that are necessary to manufacture a quality product, and to ensure that appropriate procedures are followed to ensure that risks to the patient in the manufacturing systems are adequately controlled
- The term Quality Unit is used as an encompassing term that includes many quality-related roles, including those responsibilities covered by the role of Qualified Person (as defined in Article 51 of 387 EU Directive 2001/83/EC)

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GUIDE CONTENT

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SCIENCE-BASED APPROACH

- Scientific knowledge should be the basis on which risk assessments performed to support design, development, and verification to ensure that pharmaceutical systems are suitable for intended use
- Identification of the CPPs and CQAs, along with defined appropriate operating limits or acceptance criteria, should be included in the documented product development data, process flow diagram, and product quality strategy
- Product and process requirements should be used to define appropriate verification activities and acceptance criteria to ensure that manufacturing elements are suitable for their intended use

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QUALITY RISK MANAGEMENT IN THE LIFE CYCLE

- QRM should underpin the specification, design, and verification process, and be applied appropriately at each stage
- Two primary principles of quality risk management are identified in ICH Q9:
  - 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

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QUALITY BY DESIGN

- Quality should be built into the design throughout the specification, design, and verification process.
- Assurance that manufacturing elements are suitable for intended use should not rely solely upon verification after installation.
- The process control strategy is essential to the overall product quality control strategy:
  - to mitigate process risks by design
  - to control risks via the process control strategy
  - to detect failure of the process to meet critical to quality aspects by measurement, alarming and action as part of an overall product quality control strategy limits

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SPECIFICATION AND VERIFICATION

- The process of specification, design, and verification of equipment and systems should include the following activities:
  - requirements definition
  - specification and design
  - verification
  - acceptance and release
- GEP, QRM, and design reviews should be applied throughout the process and throughout the lifecycle

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GOOD ENGINEERING PRACTICE

- GEP is defined as established engineering methods and standards that are applied throughout the project life cycle and ensure the effective satisfaction of stakeholder requirements
- They deliver appropriate, cost-effective solutions to meet user requirements and compliance with all applicable regulations
- GEP should be applied to all stages of the specification, design, and verification process
- GEP ensures that an engineering project meets the requirements of the user while being cost effective, compliant with regulations, and well documented. Established guidance and standards support effective GEP.
- For GMP projects, it is critical to the overall project success, that the principles of GEP are applied with the full cooperation of suppliers, engineering and construction companies, and an organization's own cross-functional teams.

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CONTINUAL IMPROVEMENT

- Once the verification process is completed, the system will be subject to the appropriate quality system(s) for ongoing support and continual improvement
- An evaluation should be performed periodically or upon specific incidents, such as frequent non-conformance of the system or product, to review the performance of the system and its ability to continue functioning as required to meet critical aspects of manufacturing capability. The review should confirm that the system remains suitable for intended use or recommend potential improvements
- Where system improvements are recommended, this Guide may assist in their appropriate design and implementation

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CHANGE MANAGEMENT

- Change Management practices should be appropriate to the activities performed and the stage within the system life cycle
- Change Management practices may, generally, be identified as:
  - engineering change management, based upon GEPs
  - formal QA change control, using similar GEPs augmented with pre- and post- approvals by the Quality Unit, is required during commercial manufacturing
- Implementing formal QA Change Control, with Quality Unit pre and post approvals, prior to starting commercial manufacturing operations is unlikely to provide benefit

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SUBJECT MATTER EXPERTS

- Subject Matter Experts (SMEs) are defined as those individuals with specific expertise in a particular area or field
- SMEs should take the lead role in the verification of manufacturing elements
- SME responsibilities include planning and defining verification strategies, defining acceptance criteria, execution of verification tests, and reviewing results
- SMEs are encouraged to understand, identify, and leverage best practices and processes related to automated equipment system.

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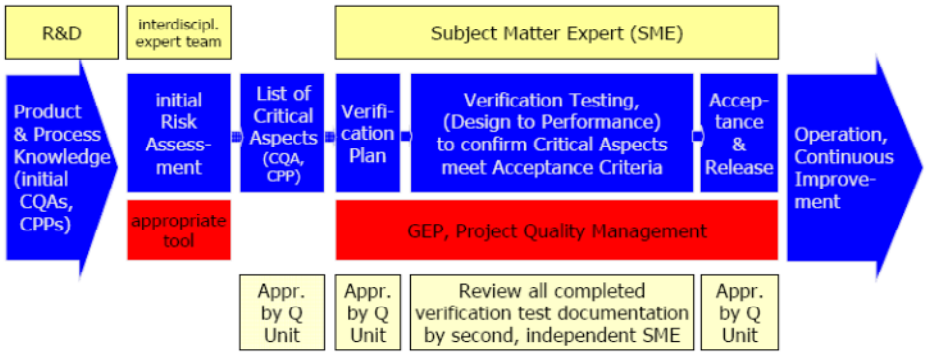
The Risk-Based Verification Process



CPP: Critical Process Parameter
CQA: Critical Quality Attribute

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SUPPLIER MANAGEMENT

- Use of supplier documentation, inspection results, and test results can help to reduce duplication of effort
- In the case of supplied equipment or systems with critical aspects, appropriate SMEs should assess the QMS of the supplier to determine whether, and the extent to which, supplier documentation, inspections, and test results can be leveraged
- The regulated organization should establish a clear approach for ensuring that the fabricated and delivered system or equipment complies with the pre-established requirements
- The regulated organization should establish how compliance is verified and documented during verification testing and performance testing

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AUTOMATION

- Automation should be an integral part of the verification process for a manufacturing system that takes into account systems, process flows, automation and equipment elements of the system, as well as other functions such as data flow, alarming, and reporting
- Once critical aspects of manufacturing, their acceptance criteria, and the verification plan are in place, the development and testing of the automation, both in the development environment and the production environment, become engineering activities
- Verification activities may help determine actual operating ranges within which the system is capable (process capabilities)

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Commissioning

- "Commissioning is a managed and planned process of bringing a facility or equipment from its installed or constructed state into operational service. This normally involves a process of setting to work followed by regulation and adjustment. These activities should be based on the principles of GEP. Commissioning activities are based on the principles of GEP and it should be a well planned, executed, and documented process
- Commissioning is a process executed by engineers, which applies to all aspects of a facility, equipment, and services. The key activities are similar regardless of whether commissioning is applied to a new facility or a simple piece of equipment has been constructed and installed; only the complexity is different. Key activities include:
  - planning
  - schedule
  - inspection and testing
  - report

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"Qualification"

- The term "qualification" may continue to be used
- "q*ualification"* should mean that equipment has been found to be suitable for its intended use, based on:
  - the design criteria (process requirements or equivalent necessary to manufacture a quality product)
  - demonstration of sufficient control of risks to the patient
  - documentation compiled through the verification work performed throughout the delivery process and life cycle
- This does not imply the necessity to conduct additional work in the form of separate DQ, IQ, and OQ protocols – the definition of DQ, IQ, and OQ is based on providing "documented verification." This guide recommends a compliant yet efficient method of producing this verification evidence

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Verification

- Defined in Verification Plan(s)
  - Scope of work
  - Verification strategy
  - Acceptance criteria for critical aspects
  - Documentation requirements
- Verification Testing (Phases)
  - Design Reviews
  - Factory Acceptance Testing (FAT)
  - Site Acceptance Testing (SAT)
  - Installation Verification (IV)
  - Functional Verification (FV)
  - Performance Testing (PT/PQ)

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Common GEP Practices

- Good Documentation Practices (GDP)
- Engineering Project Change Management
- Project Audits
- Planning Related Activities
  - Project Planning
  - Quality Planning
  - Communication Plan
  - Procurement Plan
- Design Reviews
- Management Systems
- Construction Quality Standards
- Project Site Logistics
- Project Quality Control
- Non GMP Regulation Compliance
- Turnover and Project Closure

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Verification – ASTM E2500-07

- It is a life-cycle approach – not a check at the end of the process
- It is based on the process and product knowledge, regulatory, and quality standards
- Verification approach must be documented – Verification Plan(s) (approved by quality unit)
- Acceptance criteria must be established
- Documented confirmation that the equipment/system is fit for intended use
- Acceptance and release must be documented (approved by the quality unit)

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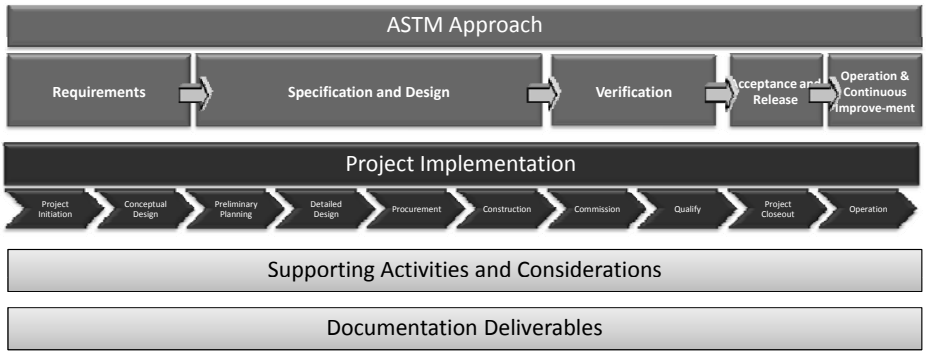
Flow Chart / Diagram the Process



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An Employee-Owned Company

Thank You!

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