Effective Integration of Quality Risk Management (QRM) from Specification and Design Through Successful Verification

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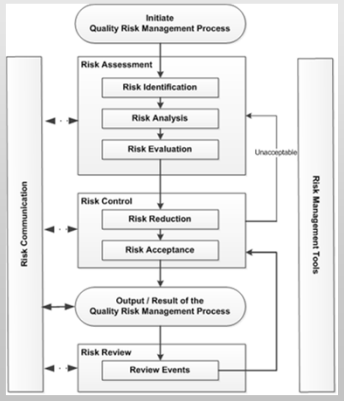
Review of Core concepts and Principles



Quality by Design (QbD): A systematic approach to development that begins with predefined objectives and ***emphasizes product and process understanding*** and process control, based on sound science and quality risk management. (ICH Q8 (R2))

Quality Risk Management (QRM): Quality risk management is a systematic process for the assessment, control, communication and review of risks to the quality of the drug (medicinal) product across the product lifecycle. (ICH Q9)

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Review of Core concepts and Principles

Product:

Critical Quality Attribute (CQA): A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. (ICH Q8 (R2))

Process:

Critical Process Parameter (CPP): A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. (ICH Q8 (R2))

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Review of Core concepts and Principles

Manufacturing Systems: Elements of pharmaceutical and biopharmaceutical manufacturing capability, including manufacturing systems, facility equipment, process equipment, supporting utilities, associated process monitoring and control systems, and automation systems, that have the potential to affect ***product quality and patient safety***.

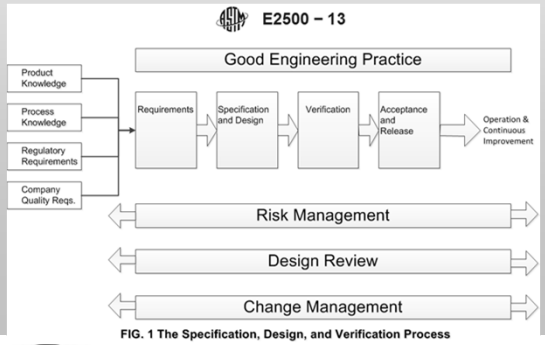

FIG. 1 The Specification, Design, and Verification Process

Critical Aspects: Are typically functions, features, abilities, and performance or characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. They should be identified and documented based on scientific product and process understanding.

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THE starting Point: Understanding ***Product and Process Requirements***

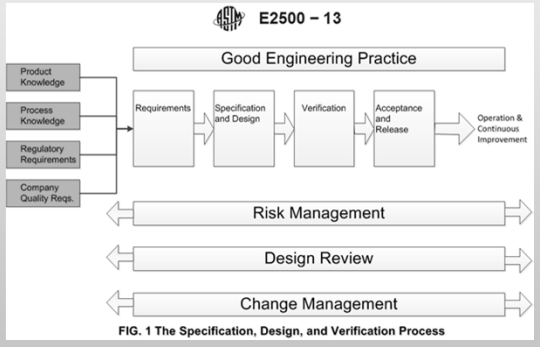

FIG. 1 The Specification, Design, and Verification Process

Example: Product/Process Requirements

We need a new skid for processing two similar but different products.

A Commercial Process Description (CPD) for Product X lists flow rate as a **CPP** during a mixing step, the NOR is 40-60 lpm the PAR is 35-70 lpm

The CPD for Product Y lists flow rate as a **CPP** during mixing, the NOR is 55-65 lpm the PAR is 55-80 lpm

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Develop system requirements to satisfy ***Product and Process Requirements***

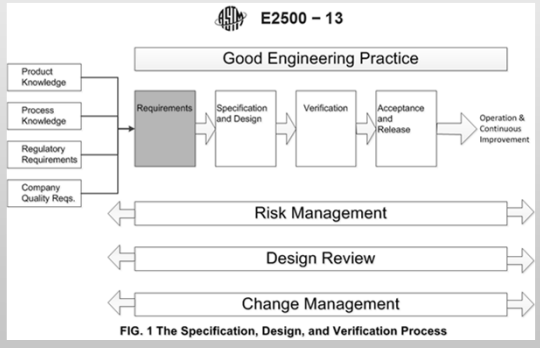

FIG. 1 The Specification, Design, and Verification Process

Example: System Requirements

The system must provide a flow rate of 35-80 lpm during mixing.

Once System Requirements are drafted a Design Review of the System Requirements against Product and Process Requirements (P/PRs) in the CPD's for Products X and Y should be performed to ensure System Requirements satisfy P/PRs as a stage gate to approving System Requirements.

A high level Risk Assessment (e.g. PHA) may be performed to focus future QRM activities as the design progresses.

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Develop system requirements to satisfy ***Product and Process Requirements Example Trace Matrix***

Process Stage	Process Step	CPP	NOR	PAR	Ref.	System Requirement	Ref.
Product X – Solution Prep.	Mixing	Flow Rate	40 – 60 lpm	35 – 70 lpm	CPD - X	The system must provide a flow rate of 35 – 80 lpm during mixing.	URS
Product Y – Solution Prep.	Mixing	Flow Rate	55 - 65 lpm	55 - 80 lpm	CPD - Y		

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Develop system requirements to satisfy ***Product and Process Requirements***

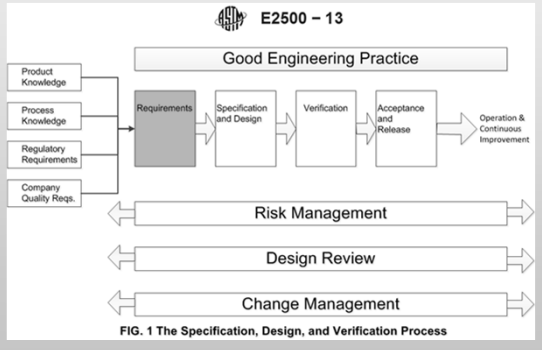

FIG. 1 The Specification, Design, and Verification Process

Example: System Requirements

System Requirements should be reviewed and approved by **Quality and Validation**, since all future design efforts will be reviewed to ensure the system design satisfies system P/PRs.

Future Qualification efforts will focus on ensuring the system satisfies approved P/PRs.

Once approved, System Requirements should be subject to Engineering Change Management (ECM).

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Specify and design the system to satisfy approved system P/PRs

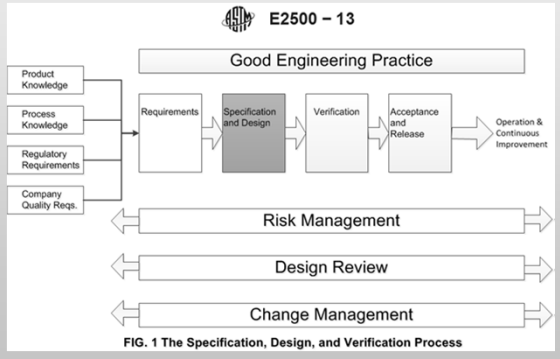

FIG. 1 The Specification, Design, and Verification Process

Example: System Design

System Specification and Design should utilize Good Engineering Practice (GEP).

GEP includes the use of approved engineering standards and methods (e.g. company approved sanitary piping specs, automation standards, etc.).

While QRM activities are focused on product quality and patient safety, GEP activities should also focus on safety, operability, reliability, cost, etc.

QRM based Design Review and Risk Assessments (DR/RA) are not intended to take the place of GEP activities such as peer review or confirming engineering calculations.

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Specify and design the system to satisfy approved system P/PRs

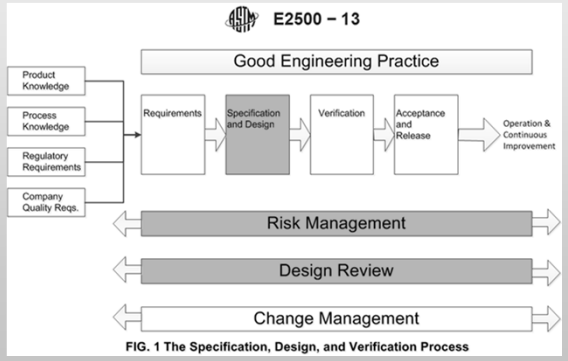

FIG. 1 The Specification, Design, and Verification Process

Example: System DR/RA

System DR/RA should be performed at appropriate design stages to ensure that:

- P/PRs are satisfied by the system design
- Critical Aspects of the manufacturing system are appropriately addressed (e.g. identified and defined)
- Risks to product quality and patient safety have been identified
- Unacceptable risks are identified and mitigated by design or other methods
- A Verification strategy is established

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Specify and design the system to satisfy approved system P/PRs

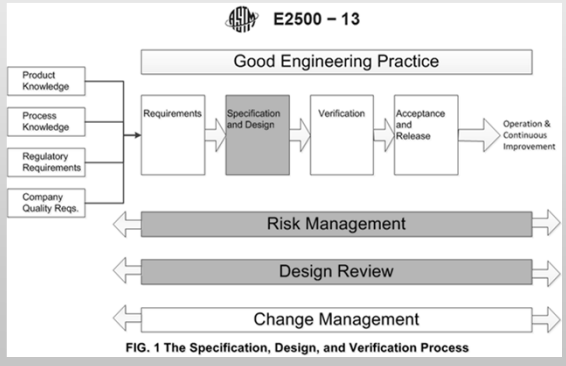

FIG. 1 The Specification, Design, and Verification Process

Example: System DR/RA

System DR/RA should be performed as a collaborative effort by SMEs including **Quality and Validation.**

DR/RA forms the true bridge between Engineering and Quality, since quality is designed in and risk to product quality and patient safety are addressed before any testing takes place.

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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

Example: System Requirement

The system must provide a flow rate of 35-80 lpm during mixing.

Example: Critical Aspects

Primary Critical Aspect:

- Flow Control Loop F-14

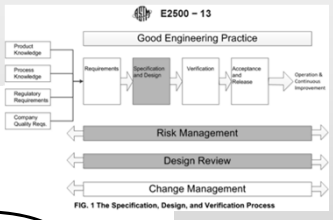
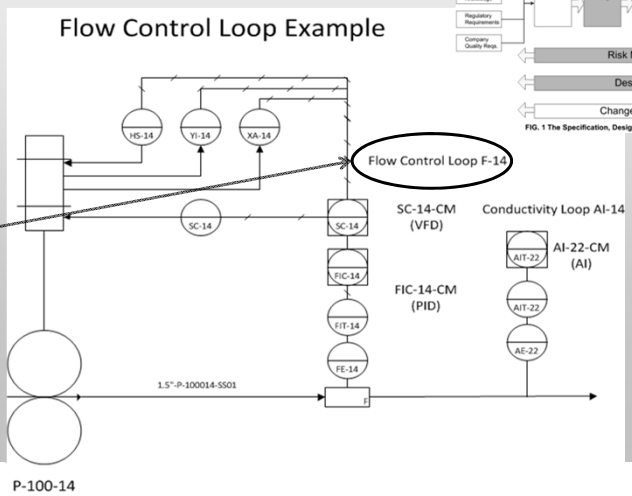


FIG. 1 The Specification, Design, and Verification Process



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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

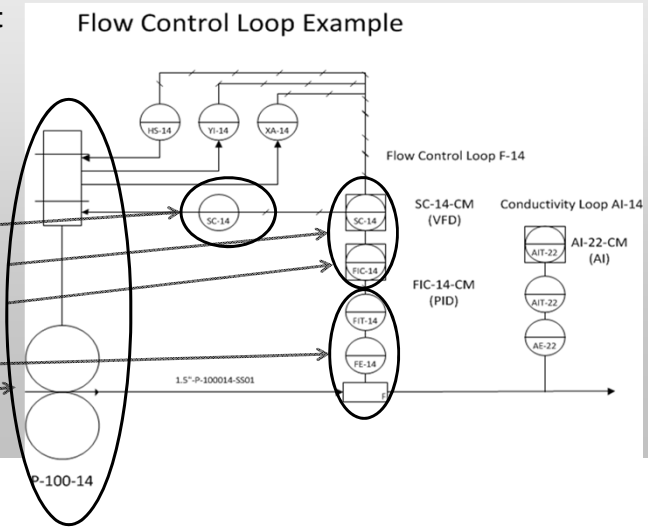
Example: System Requirement

The system must provide a flow rate of 35-80 lpm during mixing.

Example: Critical Aspects

Secondary Critical Aspects:

- Speed controller/VFD SC-14
- Automation: VFD Control Module SC-14-CM
- Automation: PID Control Module FIC-14-CM
  - High/Low Flow Alarms
- Flow instrument loop FE/FIT-14
- Pump P-100-14



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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

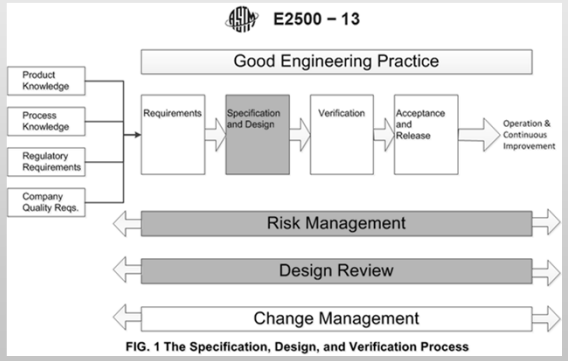

FIG. 1 The Specification, Design, and Verification Process

The applicable design specifications of the Critical Aspects should be reviewed by Engineering SMEs to ensure the design satisfies approved System P/PRs

This review should be documented along with the relevant design specifications. This is typically documented in a trace matrix.

Designs that do not satisfy System P/PRs should be modified accordingly.

Example: Incorrect pump curve for the required flow rates requires specifying a new pump

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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

System Requirement	Ref.	Critical Aspects			
		Number	Description	Specification	Ref.
The system must provide a flow rate of 35 – 80 lpm during mixing.	URS	CA-001	Flow Control Loop F-14	Controls flow rate in skid from 10-100 +/- 0.05 lpm	P&ID
		CA-001a	Speed controller/VFD SC-14	1 phase, 208V, 50/60Hz Range 1-120 +/- 0.01 Hz Over/Under voltage protected	P&ID, data sheet
		CA-001b	VFD Control Module SC-14-CM	Provides output logic, display, alarming, historian functions to control VFD based on PID input	P&ID, Configuration Spec SC-14-CM
		CA-001c	PID Control Module FIC-14-CM	Provides output, logic, display, alarming, historian functions based on input from FE/FIT-14	P&ID, Configuration Spec FIC-14-CM
		CA-001d	Flow instrument loop FE/FIT-14	Range 0-150 lpm Accuracy 0.25% of full range	P&ID, Instrument data sheet
		CA-001e	Pump P-100-14	Max Flow: 140 lpm Max Pressure: 4.3 bar Single Use pump head	Data sheet

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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

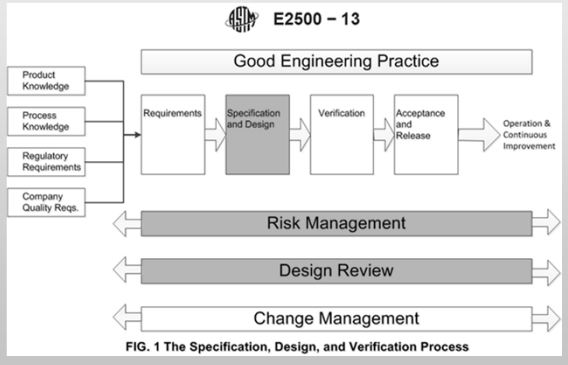

FIG. 1 The Specification, Design, and Verification Process

Once the design has been reviewed (e.g. Critical Aspects identified & design confirmed to satisfy System P/PRs) a risk assessment should be performed.

This risk assessment should assess how the system design can fail (specifically the Critical Aspects). Typically an FMEA is used since the design information should be substantially complete and a quantitative assessment can be accomplished.

Unacceptable risks should be identified and mitigated by design or other methods.

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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

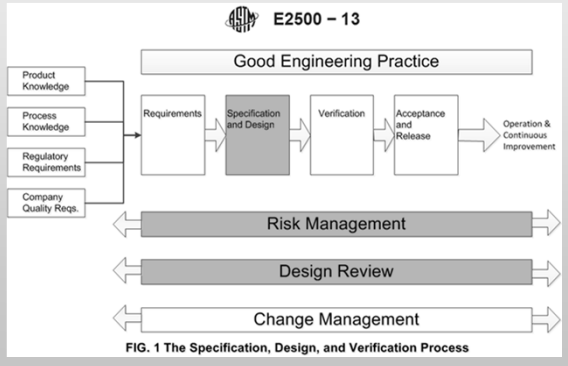

FIG. 1 The Specification, Design, and Verification Process

Example: Through prior SME knowledge of similar designs and instrumentation, flow instrument loop FE/FIT-14 is prone to drift. This causes an unacceptable risk since "occurrence" is high and "detection" is poor.

Mitigation Option#1: Change the design by upgrading the FE/FIT

Mitigation Option#2: Add an independent FE/FIT loop to detect drift (e.g. difference alarm)

Mitigation Option#3: Increase the instrument loop calibration frequency

Mitigation Option#4: All of the above

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Specify and design the system to satisfy approved system P/PRs: ***Example DR/RA***

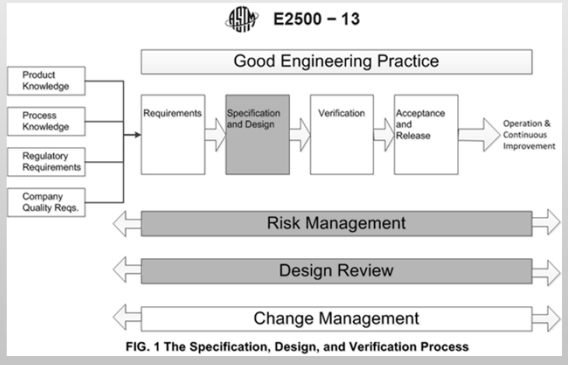

FIG. 1 The Specification, Design, and Verification Process

During DR/RA the general verification strategy for Critical Aspects should be developed, reviewed and approved collaboratively by SMEs including **Quality and Validation.**

The approved verification strategy should be documented (typically in a trace matrix).

The verification strategy should define what type of testing is required for Critical Aspects, i.e.:

- Development Testing
- FAT/SAT
- Commissioning
- Qualification
- Combined
- Leveraging

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Verification: ***Example verification model***

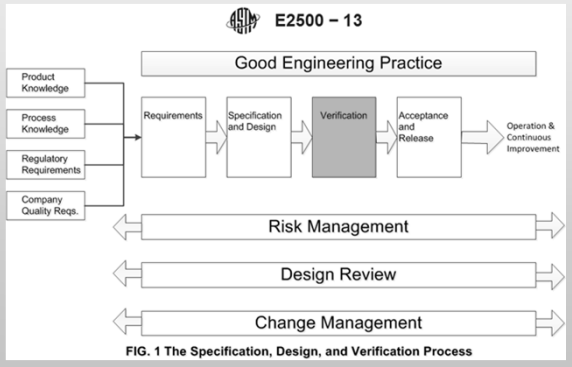

FIG. 1 The Specification, Design, and Verification Process

A variety of verification approaches can be used to confirm a manufacturing system is fit for it's intended use.

For this example Qualification with Quality approval is used to demonstrate that **the system satisfies the approved System P/PRs**.

As a result, Qualification (IQ/OQ) will focus on the primary Critical Aspect

Secondary Critical Aspects would primarily be verified with GEP type testing (e.g. Commissioning).

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Verification: ***Example verification model***

Critical Aspects				Verification Method
Number	**Description**	**Specification**	**Ref.**	
CA-001	Flow Control Loop F-14	Controls flow rate in skid from 10-100 +/- 0.05 lpm	P&ID	Functionally test control loop over entire specified range in CTP **Challenge control loop over P/PR range in IOQ**
CA-001a	Speed controller/VFD SC-14	1 phase, 208V, 50/60Hz Range 1-120 +/- 0.01 Hz Over/Under voltage protected	P&ID, data sheet	Verify proper installation against drawings, verify make, model, record serial number in CTP Verify configuration and functionally test in CTP
CA-001b	VFD Control Module SC-14-CM	Provides output logic, display, alarming, historian functions to control VFD based on PID input	P&ID, Configuration Spec SC-14-CM	Test to ensure all module components - logic, displays, historian, alarms, etc. are functioning individually and together during DT or CTP
CA-001c	PID Control Module FIC-14-CM	Provides output, logic, display, alarming, historian functions based on input from FE/FIT-14	P&ID, Configuration Spec FIC-14-CM	Test to ensure all module components - logic, displays, historian, alarms, etc. are functioning individually and together during DT or CTP
CA-001d	Flow instrument loop FE/FIT-14	Range 0-150 lpm Accuracy 0.25% of full range	P&ID, Instrument data sheet	Verify proper installation against drawings, verify make, model, record serial number in CTP Verify configuration of associated control modules in CTP Verify instrument is in CMMS and has current calibration label in CTP
CA-001e	Pump P-100-14	Max Flow: 140 lpm Max Pressure: 4.3 bar Single Use pump head	Data sheet	Verify proper installation against drawings, verify make, model, record serial number in CTP Functionally test in CTP

Verification: ***Example verification model***

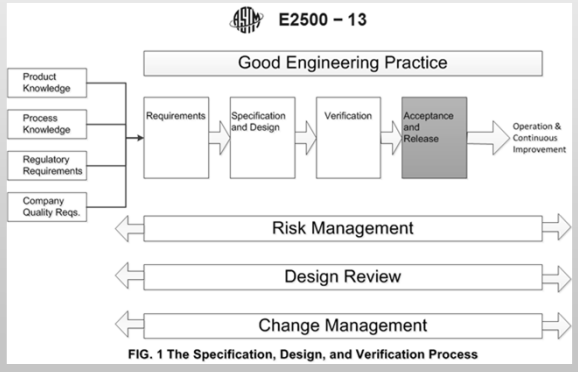

FIG. 1 The Specification, Design, and Verification Process

Upon successful completion of verification testing (both GEP and Qualification) references to actual testing should be documented, typically in a trace matrix.

A Qualification summary report should summarize the results of qualification testing.

It should contain a clear statement as to whether or not the system and it's Critical Aspects satisfy approved acceptance criteria and, as a result, approved P/PRs.

A Qualification summary report should be reviewed and approved by Quality.

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System Acceptance and release

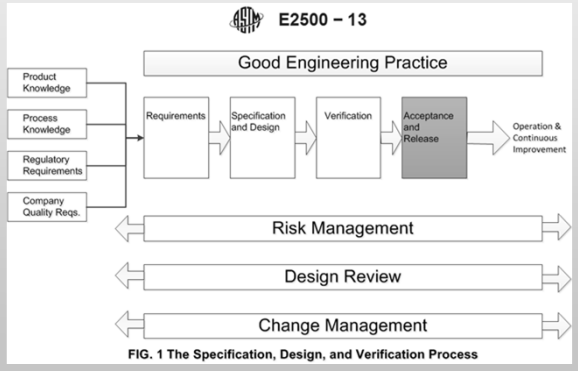

FIG. 1 The Specification, Design, and Verification Process

Acceptance and Release of the system from the engineering phase to the operational phase of it's life cycle should be a formal process with Quality oversight.

Typically, a brief report containing a clear statement that the system is fit for it's intended should be generated and approved.

The Qualification summary report should not be the only document used for Acceptance and Release.

Other GEP and QRM activities and documents should be considered.

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System Acceptance and release

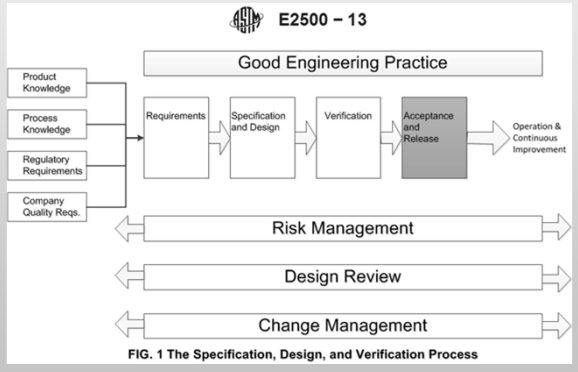

FIG. 1 The Specification, Design, and Verification Process

Quality/QRM activities/documents typically required for Acceptance and Release include, but may not be limited to:

- ✓ System Requirement document (s) (e.g. URS) is approved
- ✓ System DR/RA is complete and approved (including actual references to verification activities)
- ✓ System Qualification is successfully completed and approved

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System Acceptance and release

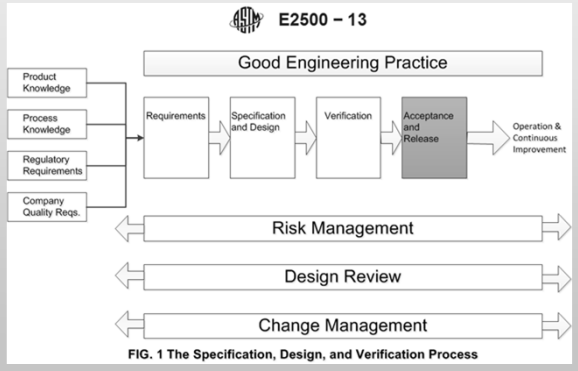

FIG. 1 The Specification, Design, and Verification Process

GEP activities/documents typically required for Acceptance and Release include, but may not be limited to:

- ✓ System drawings updated and approved
- ✓ System design specifications approved
- ✓ System verification testing complete and approved
- ✓ PM and calibration program is in place for the system

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ASTM E2500 as a framework for QbD and QRM

Benefits:

- ✓ Clear rationale for validation, tied directly back to product quality and patient safety
- ✓ Focused quality systems in operational phase of system life cycle (e.g. change controls, deviations, etc.)
- ✓ Quality oversight and involvement from requirements definition through system release, not just approval of end testing
- ✓ Continuous verification throughout system design

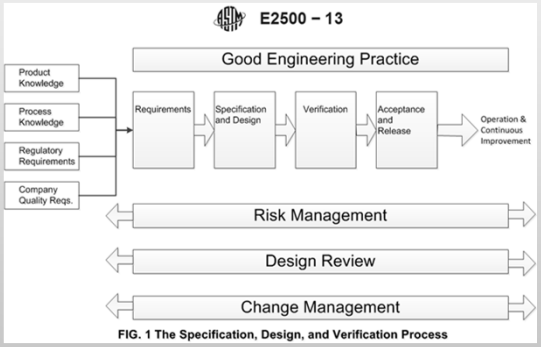

FIG. 1 The Specification, Design, and Verification Process

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ASTM E2500 as a framework for QbD and QRM

Pitfalls and Lessons Learned:

- ✓ Implementing an ASTM E2500 framework can expose a lack of GEP
- ✓ Design development should not be done concurrently with DR/RA
- ✓ Understanding, clearly stating and approving P/PRs, quality and regulatory requirements is pivotal to success. Designing to satisfy the requirements.
- ✓ Quality oversight and involvement from Requirements Definition to Acceptance and Release reinforces the bridge between Engineering and Quality

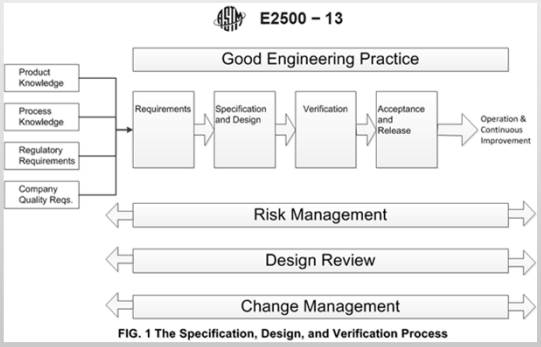

FIG. 1 The Specification, Design, and Verification Process

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PDS PROCESS DESIGN SOLUTIONS

PDS SANDBOX

Full-Service Quality by Design Solutions

Process Engineering

- Upstream/ Downstream
- SU Technology
- Process Optimization
- Process Dev./Tech. Transfer
- Automation
- System/Skid Design

Common Services

- Verification`
- Project/Program Management
- GEP Development
- Design Review
- Quality System Management
- Supplier/Vendor Assessment

Quality Risk Management

- ASTM E2500 Plan. & Implementation
- Design Review/ Risk Assessment
- QRM Program Development
- QRM Consulting
- QRM Training

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ASTM E2500 as a framework for QbD and QRM

QUESTIONS ?

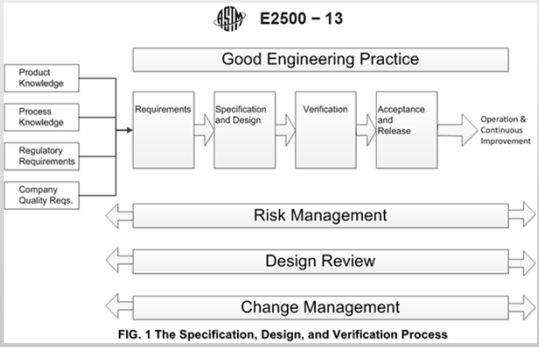

FIG. 1 The Specification, Design, and Verification Process

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