ISPE Boston Chapter Webinar

ISPE Baseline Guide Volume 5, 2nd Edition

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A Project Manager and Senior Validation Engineer, Chip is a PMI® Certified Project Management Professional (PMP) with 20 years of experience in the pharmaceutical and regulated non-pharmaceutical industries and with expertise in risk-based verification, aseptic manufacturing, cleaning validation, quality systems, and owner project management. Chip is responsible for developing and implementing Quality Risk Management (QRM) based Commissioning and Qualification programs and projects, with a focus on assessing and training clients regarding development, implementation, and transition to risk-based approaches.

Agenda

ISPE Baseline Guide Volume 5, 1st Edition
- Industry and Regulatory Drivers
- QRM Shortcomings

The Path to ISPE Baseline Guide Volume 5, 2nd Edition
- Business Drivers
- QRM as Regulatory Driver and Industry Focus

Differences Between 1st and 2nd Editions
- QRM Incorporation and Other Benefits
- Defined/Retired Terms and Activities
- Integrated C&Q Process and Deliverables
- Risk Assessment and Supporting Processes

Applying QRM to C&Q Processes

Benefits and Opportunities

Q&A

Before We Begin…

Caveats:

I am *not* a CoP steering committee member or an author/contributor to the Guide

This is *not*, and does not replace, the official CoP Presentation

About This Presentation:

More than just the content of the revised Guide

Historical context and evolution

Practical implementation based on project experience

ISPE Baseline Guide Volume 5, 1st Ed

Where were we in 2001?

ISPE Baseline Guide Volume 5, 1st Ed

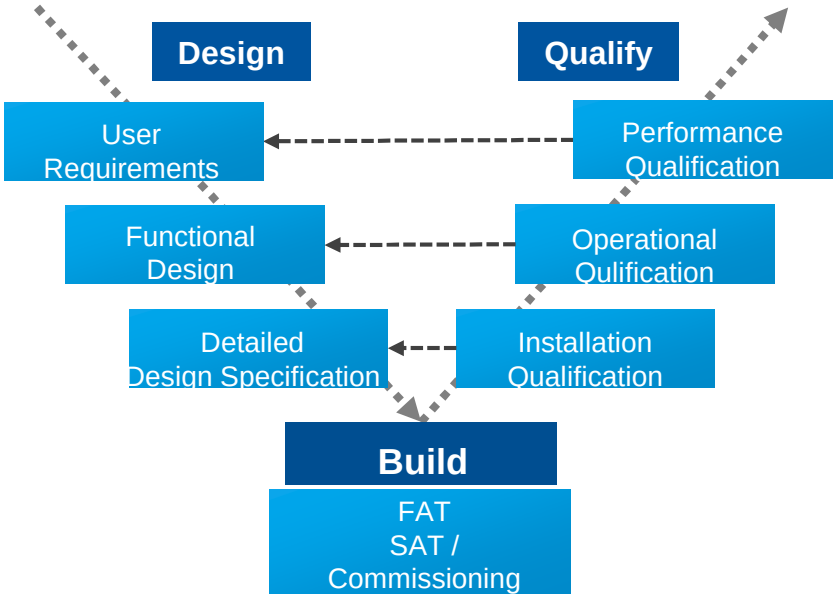
Drivers for 1st Edition:

Industry Drivers

- V-Model delivery cost, schedule, effectiveness – duplicated effort
- Inconsistent C&Q terminology
- Inconsistent interpretation of CGMP requirements

Regulatory Drivers

- Alignment with industry regarding C&Q expectations
- Consistent C&Q terminology and approach
- Focus effort on product quality, risk



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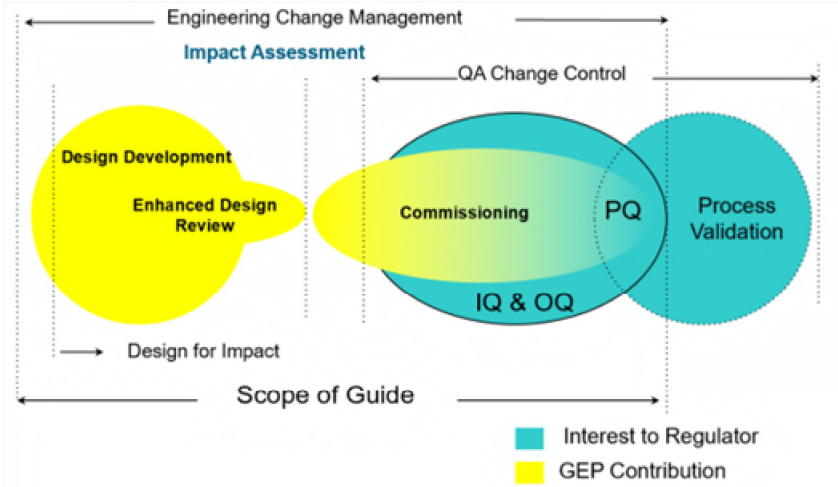
Challenges Implementing 1st Edition:



QRM Not Incorporated

- PPK (CQAs/CPPs) not understood/documented
- Risk to product quality not identified, assessed, or controlled
- Testing not commensurate with risk

Siloed Roles and Responsibilities

- Engineering and Quality roles and responsibilities overlap and contradict

Inefficient Approach

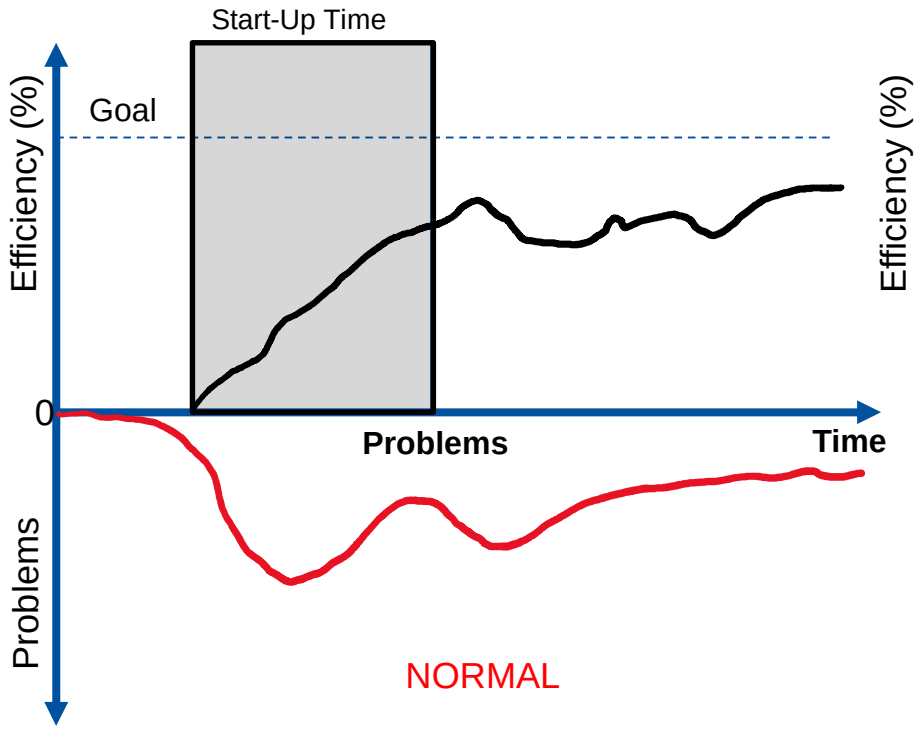
- Prescriptive testing strategy
- “Test everything” mentality
- Engineering and Qualification: non-value-added testing redundancy

Business Drivers

The path to ISPE Baseline Guide Volume 5, 2nd Ed.

ISPE Baseline Guide Volume 5, 2nd Ed

Industry Drivers: Desired Start-Up Experience: Speed to Market



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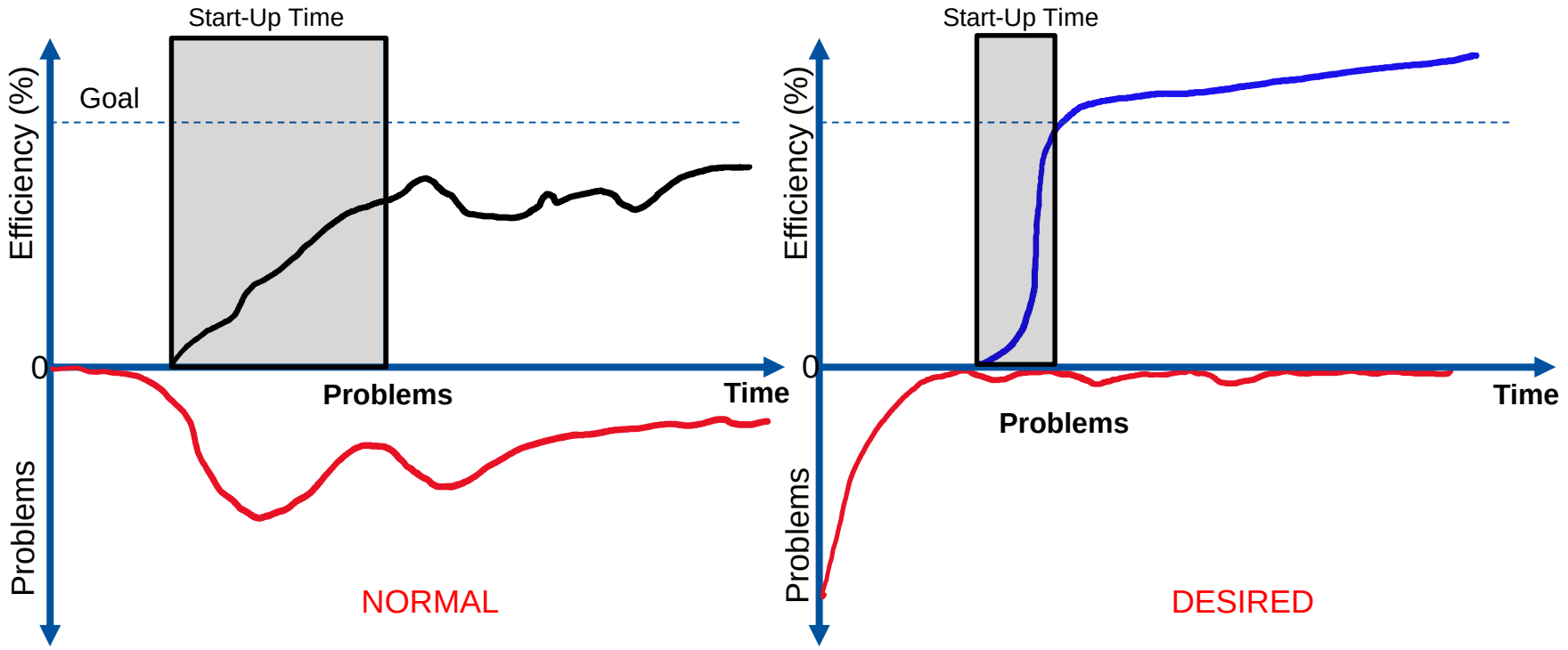
Industry Drivers: Desired Start-Up Experience: Speed to Market



Regulatory Drivers: QRM

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Regulatory Drivers: QRM

2001:

- ISPE, Baseline Guide Vol 5, 1st Ed: *Commissioning and Qualification* [C&Q Approach]

2004:

- ICH Q8, *Pharmaceutical Development* (revised 2008) [CQA, CPP, QbD]
- FDA, *Pharmaceutical Development for the 21st Century – A Risk-Based Approach*

2005:

- ISPE, White Paper: *Risk-Based Qualification for the 21st Century* [RBV Principles]
- ICH Q9, *Quality Risk Management* [QRM]

2007:

- ASTM E2500, *Spec, Design, and Ver. of Pharma/Biopharma Mfg. Sys and Equip* (rev. 2013, 2019) [RBV Process]

2011:

- ICH Q10, *Pharmaceutical Quality System* [Control Strategy]

2011:

- FDA, Guidance for Industry – *Process Validation: General Principles and Practices*
- ISPE, Guide: *Science and Risk Based Approach for the Delivery of Facilities, Systems, and Equipment*
- ISPE, Good Practice Guide 10: *Applied Risk Management for Commissioning and Qualification*

2015:

- EudraLex, Volume 4, Annex 15: *EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use*

2019:

- ISPE, Baseline Guide Vol 5, 2nd Ed: *Commissioning and Qualification* [QRM-Based Integrated C&Q]

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Regulatory Drivers: QRM

US FDA Report (2004):

Pharmaceutical Development for the 21st Century – A Risk-Based Approach

- **Innovation, QRM/Quality Systems, Risk-Based Approaches, Critical Areas, State of the Art Science**

US FDA Guidance for Industry (2011):

Process Validation: General Principles and Practices

- **QRM/Quality Systems, Risk-Based Decisions, Criticality as a Continuum, Control Commensurate with Risk, Less Reliance on Terminology**

EU EudraLex, Volume 4, Annex 15 (2015):

EU Guidelines for GMPs for Medicinal Products for Human and Veterinary Use

- **Control of Critical Aspects, QRM Approach, Risk Assessment Basis/Justification for Qualification/Validation**

QRM: Industry Focus

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Industry Focus: QRM

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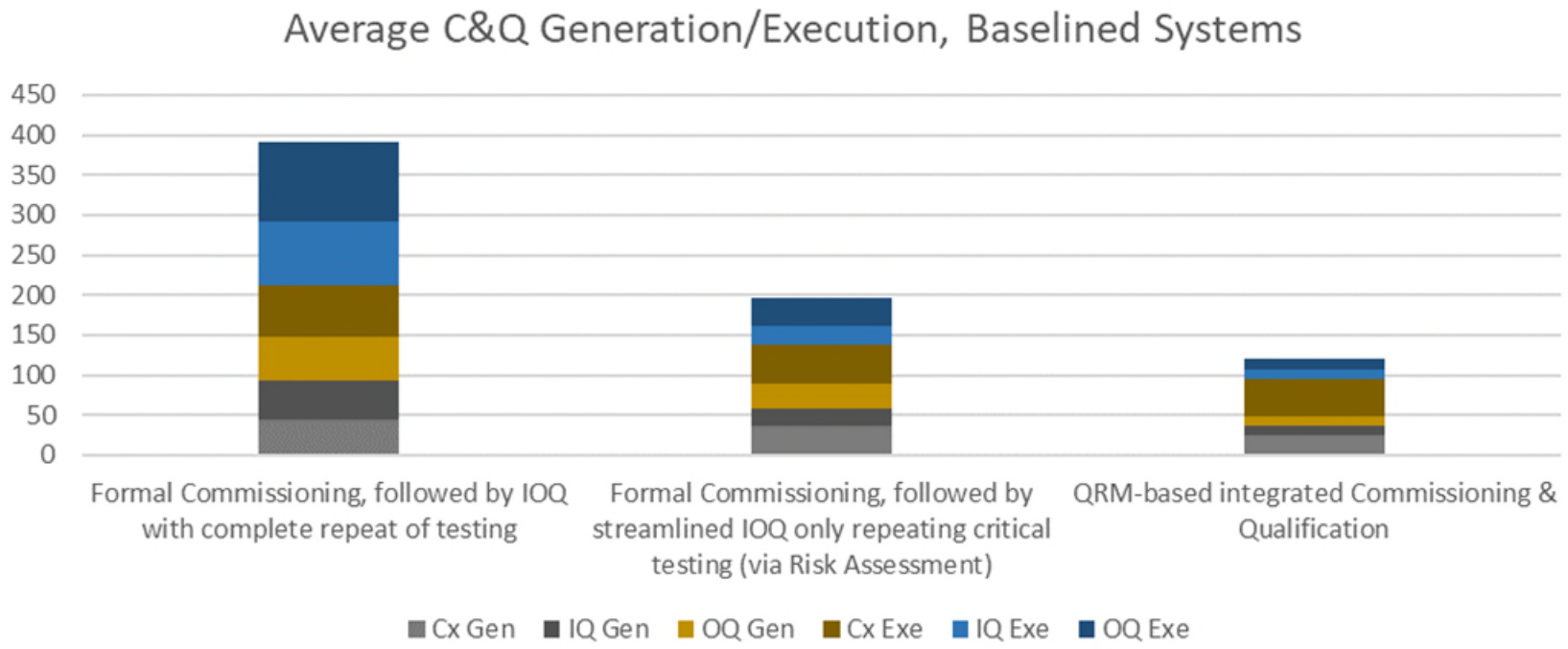
Industry Focus: QRM

CQV Benchmarking



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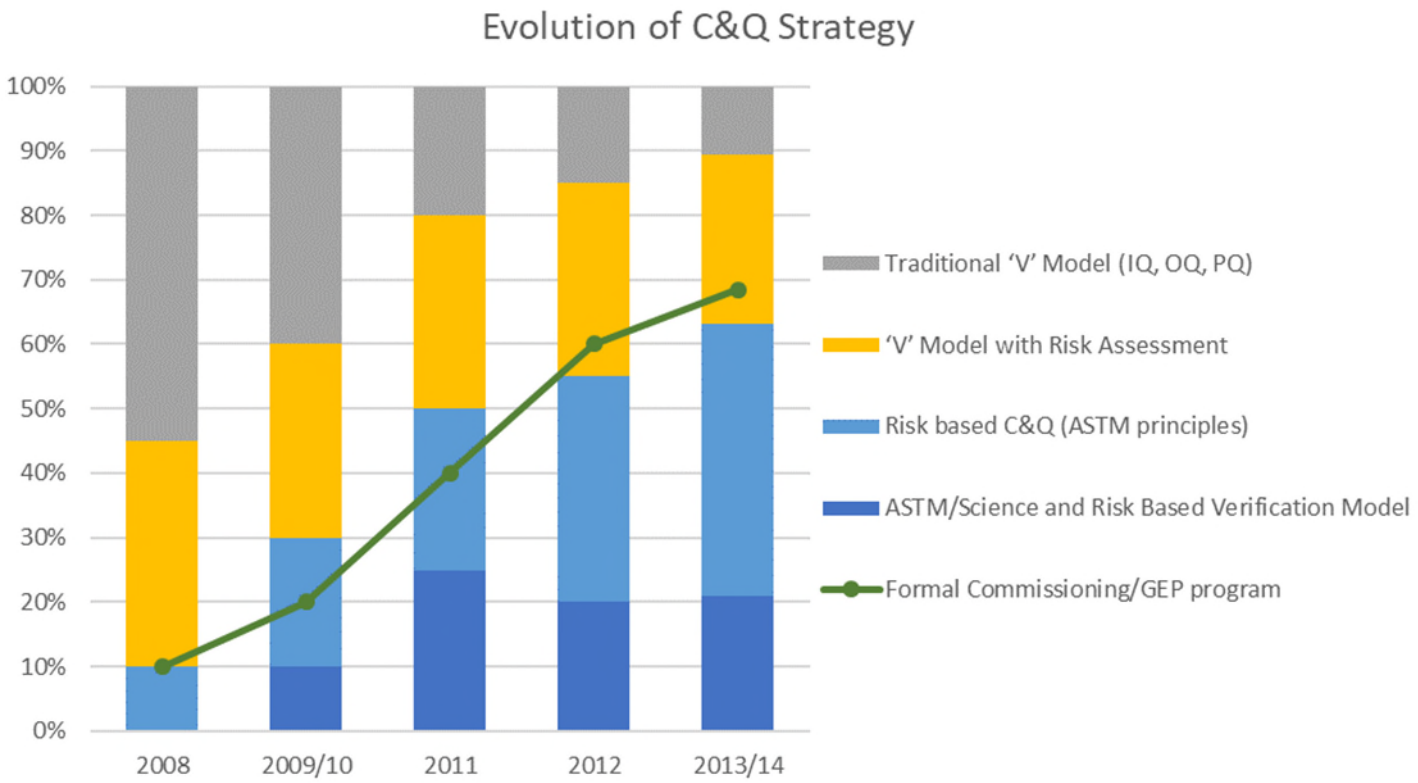
Industry Focus: QRM



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2019:

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Baseline Guide Volume 5:
1st Ed vs 2nd Ed

What has changed?

ISPE Baseline Guide Volume 5, 2nd Ed

Benefits

QRM Incorporation

Science- and Risk-Based Approach
Focus on Quality by Design (QbD)
Incorporates Industry Standards

Other Benefits

Consistent, Compliant Approach
Efficient Approach
Risk-Based Lifecycle Approach

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Defined, Retired Terms

Defined:

- Commissioning
- Qualification
- Commissioning and Qualification (C&Q)
- Validation
- Verification

Retired:

- Indirect Impact
- Component Criticality Assessment
- V-Model
- Enhanced Documentation
- Enhanced Commissioning
- Enhanced Design Review
- Leveraging

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Defined Terms

Commissioning	A well-planned, documented, and managed, engineering approach to the start-up and turnover of facilities, systems, utilities, and equipment to the end user that results in a safe and functional environment that meets established design requirements and stakeholder expectations.
Qualification	For the purpose of this guide, a ***process*** to demonstrate and document that the critical manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.
Commissioning and Qualification (C&Q)	For the purposes of this Guide, the term Commissioning and Qualification (C&Q) is used to describe the ***process*** for establishing that facilities, systems, utilities, and equipment are suitable for their intended purpose.
Validation	Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes (FDA Process Validation Guidance, 1987)
Verification	An ***activity*** that is performed within the C&Q process to document that the manufacturing facilities, systems, utilities, and equipment are suitable for the intended purpose.
Critical Design Element (CDE)	Design functions or features of an engineered system that are necessary to consistently manufacture products with the desired quality… 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.

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Defined, Retired Terms

Defined:

- Commissioning
- Qualification
- Commissioning and Qualification (C&Q)
- Validation
- Verification

Retired:

- Indirect Impact
- Component Criticality Assessment
- V-Model
- Enhanced Documentation
- Enhanced Commissioning
- Enhanced Design Review
- Leveraging

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Integrated C&Q Process

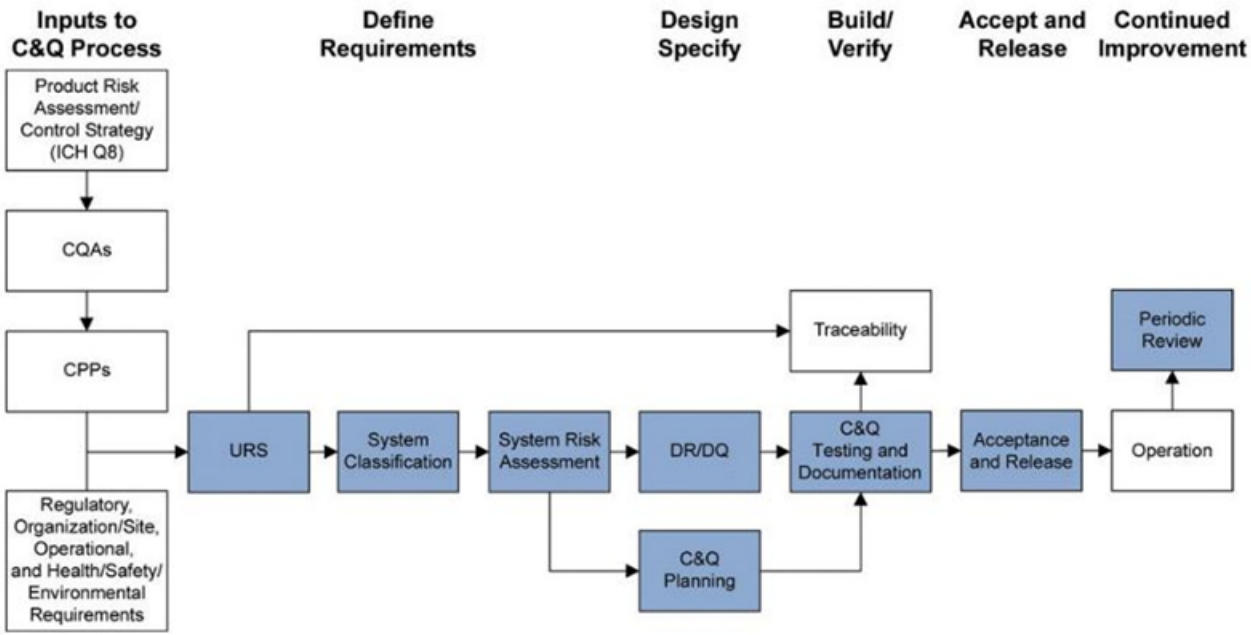

Figure 1.1: *Science and Risk-Based C&Q Process Map*

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Integrated C&Q – Roles and Responsibilities

Engineering

- Role: system delivery
- Focus: system fitness for use
- Responsibility: *verification* (testing and documentation)

Quality

- Role: product quality
- Focus: PPK, risk control strategy, system design, and verification
- Responsibility: *oversight* (approval)

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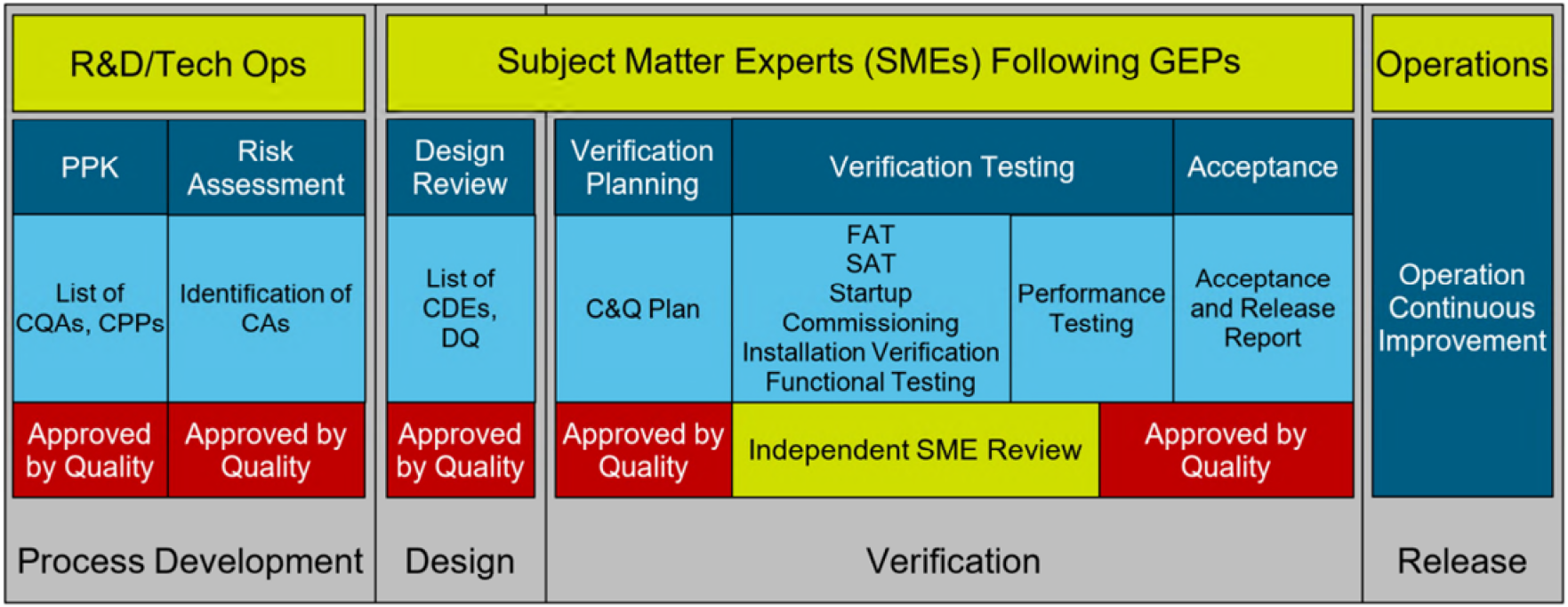
QRM-Based C&Q: Roles and Responsibilities



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QRM-Based C&Q: Roles and Responsibilities

Document	Pre-Approvers			Post-Approvers			Typical Document Preparation
	Quality	Production User	Technical	Quality	Production User	Technical	
C&Q Plan	Not applicable			A	A	A	Technical
User Requirements Specification	Not applicable			A	A	A	Technical
System Classification	Not applicable			A	A	A	Technical
System Risk Assessments	Not applicable			A		A	Quality
Design Review	Not applicable				A	A	Technical
Design Qualification	Not applicable			A	A	A	Quality
Commissioning Testing documentation, (e.g., FAT, SAT)		A	A		A	A	Technical
Qualification Testing Documentation where used	A	A	A	A	A	A	Quality
Turnover Package	Not applicable				A	A	Technical
Commissioning Acceptance and Release Report	Not applicable				A	A	Technical
Qualification Acceptance and Release Report (including Testing from Commissioning)	Not applicable			A	A	A	Quality
Traceability Matrix	Not applicable			Not applicable			Technical
Vendor Assessment	Not applicable			A		A	Technical

Quality Risk Management

Introduction and application to C&Q Processes

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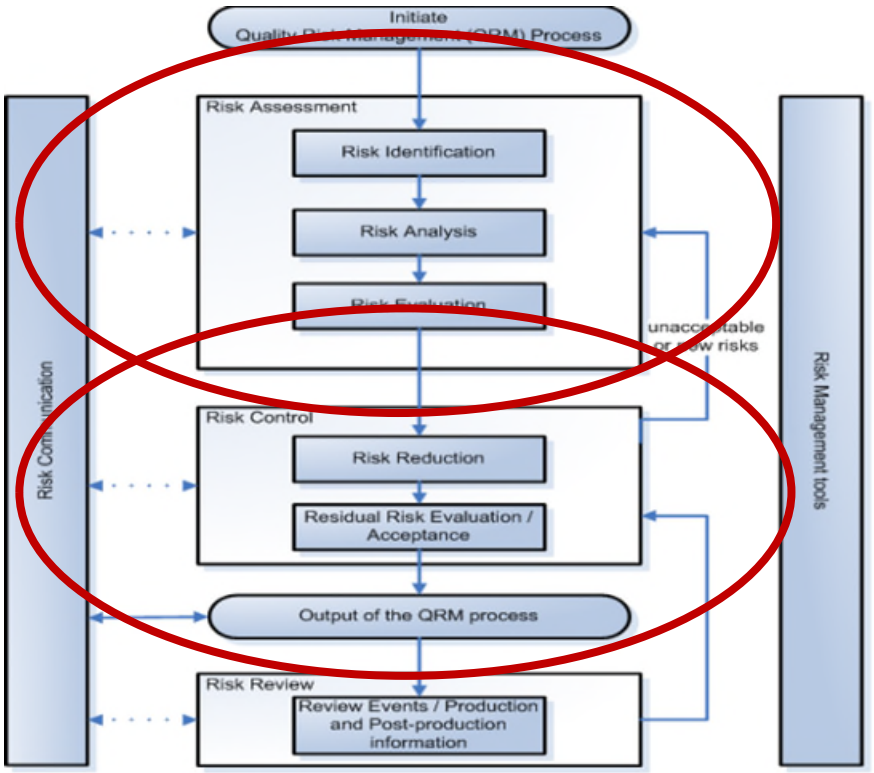
ICH Q9: QRM Process



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QRM as a Holistic Lifecycle Process

Process Development	Define Product/Process Knowledge (PPK): CQA, CPP
Risk Assessment	Identify Risks to Product Quality
Risk Control	Identify Critical Aspects (CAs) to Mitigate Identified Risks
Risk Review	Design Review: Identify CDEs / Risk Control Strategy
Quality by Design (QbD)	Design Qualification: Design of Risk Controls (CAs/CDEs) Acceptably Mitigates Risk
C&Q Strategy	Verify CAs/CDEs, Testing Rigor Commensurate w/Risk
Risk Review	Periodic Review/Revalidation, Continuous Improvement, Change Management, Deviation/CAPA Management

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Applying QRM Concepts to C&Q

Critical Quality Attribute (CQA):
Applies to the **product**.

Origin: Product and Process Knowledge (PPK)	*Risk to Product Quality* = failure to meet CQA

Critical Process Parameter (CPP):
Applies to the **process**.

Origin: Product and Process Knowledge (PPK) and Risk Assessment (RA)	*Process Risk* = failure to maintain CPP

Critical Aspect (CA):
Applies to a process **system** (*equipment, utility, facility*).

Origin: Risk Assessment (RA)	*Risk Control Strategy* = CAs collectively mitigate *unacceptable* risk to product quality

Critical Design Element (CDE):
Applies to a process system **design element** (*component, process control, alarm, etc.*).

Origin: Critical Aspects (CA) and System Design Definition	*Verification Strategy* = CDEs tested to verify installation/operation *fit for intended use*

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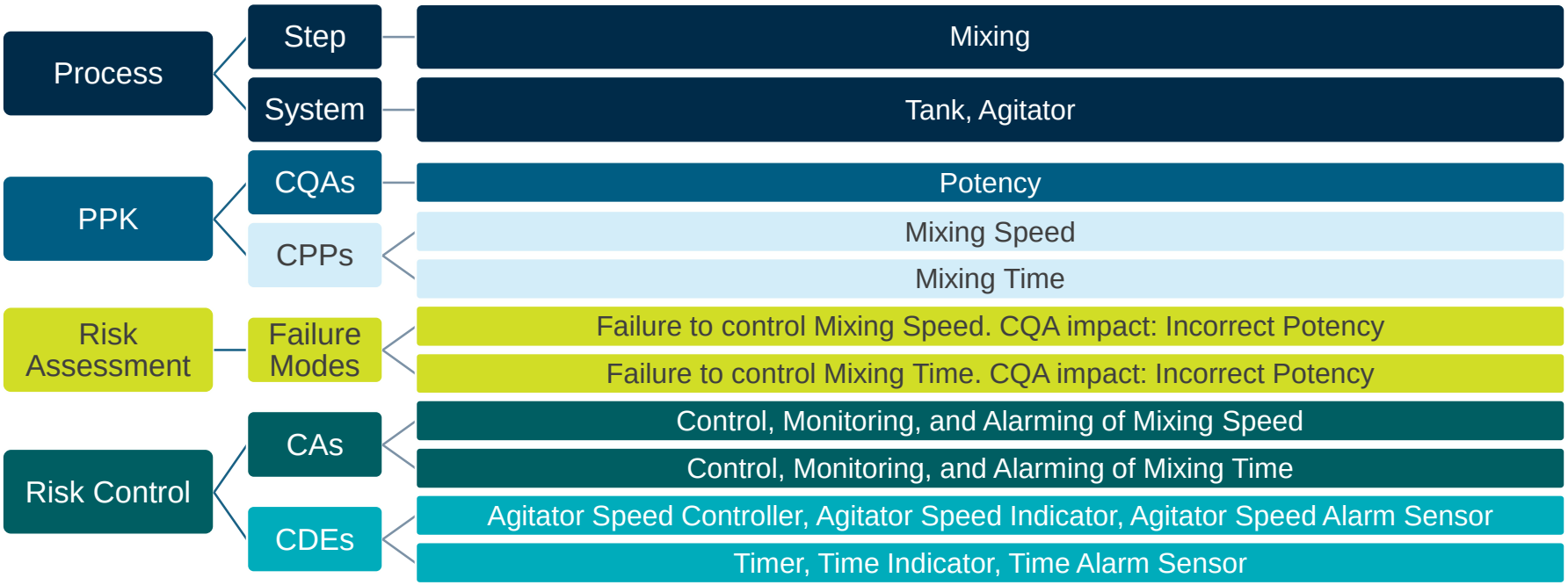
Relationship Between CQA, CPP, CA, and CDE



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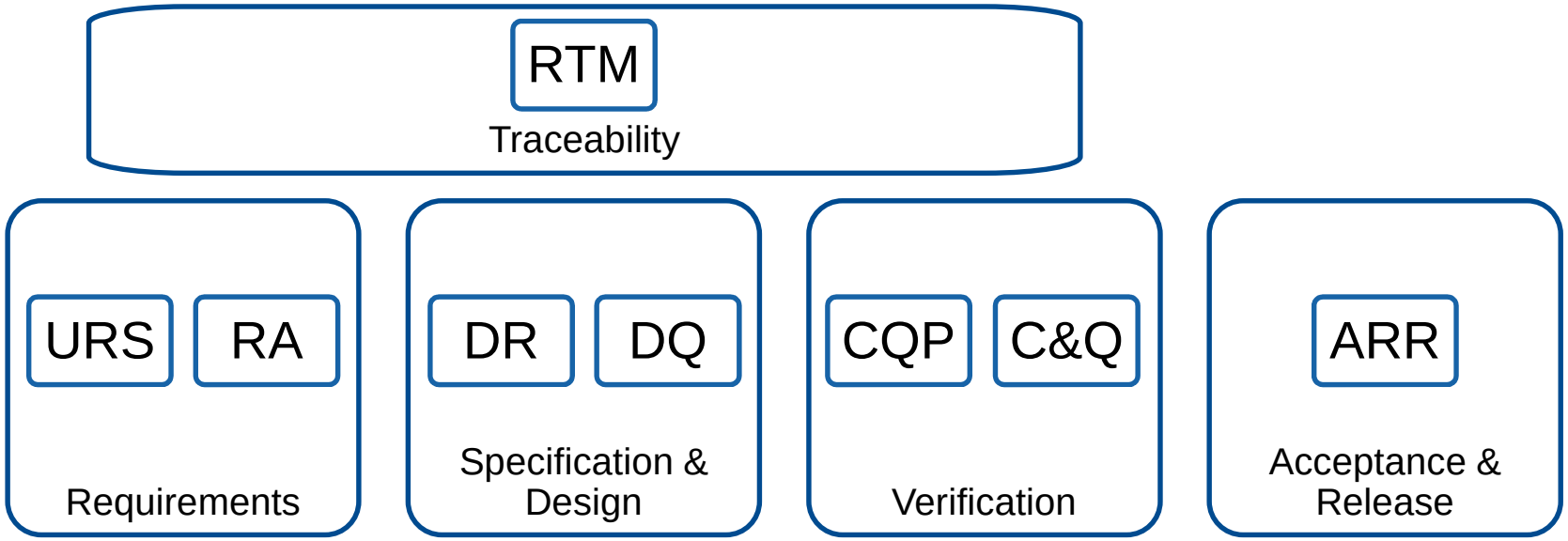
Applying QRM to C&Q Process Deliverables



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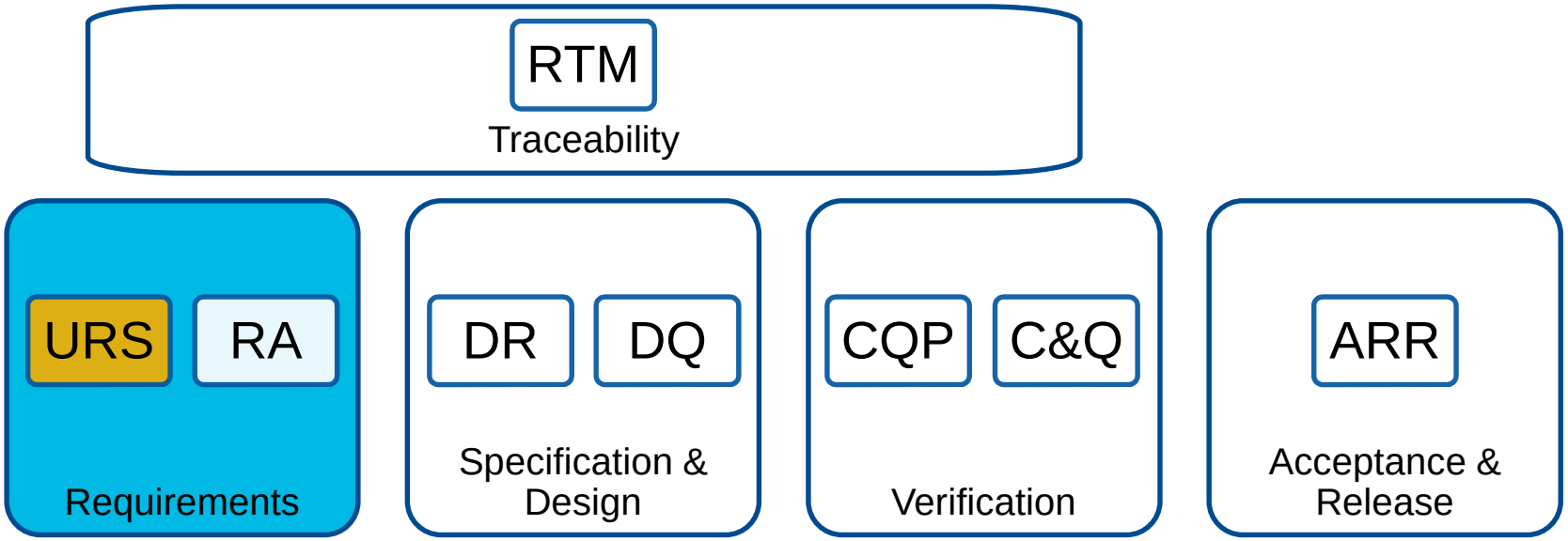

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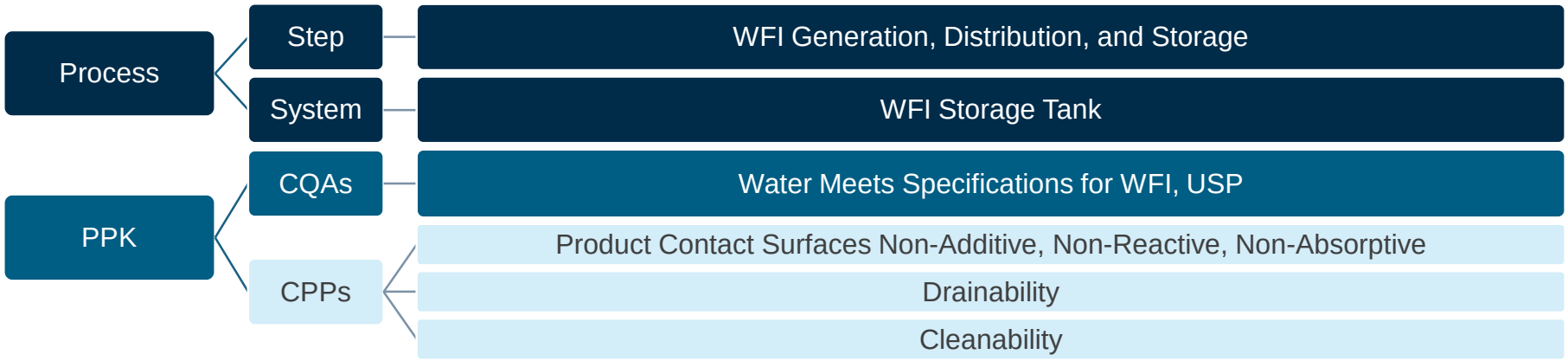

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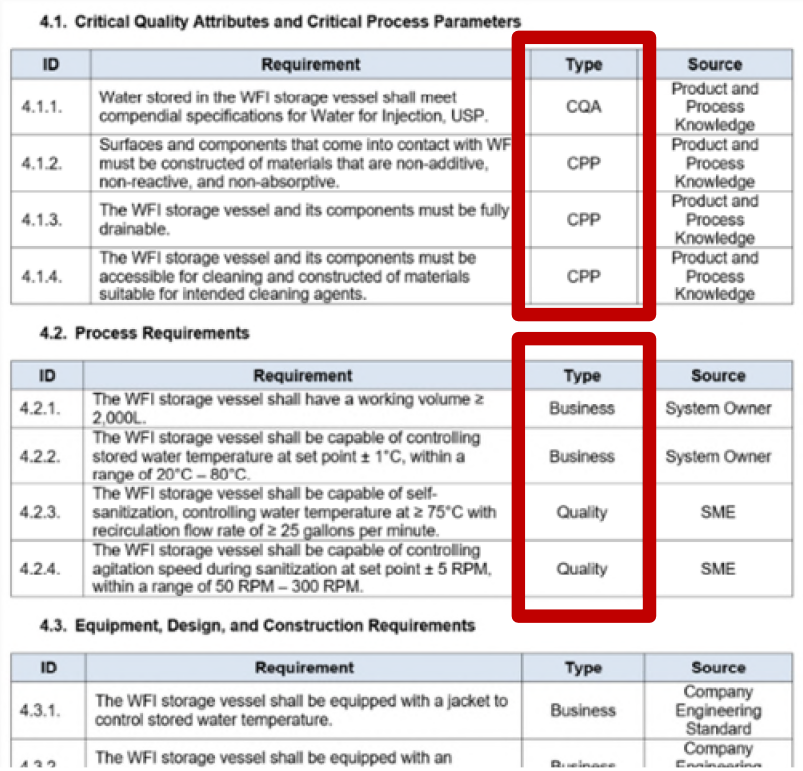

4.1. Critical Quality Attributes and Critical Process Parameters

ID	Requirement	Type	Source
4.1.1.	Water stored in the WFI storage vessel shall meet compendial specifications for Water for Injection, USP.	CQA	Product and Process Knowledge
4.1.2.	Surfaces and components that come into contact with WF must be constructed of materials that are non-additive, non-reactive, and non-absorptive.	CPP	Product and Process Knowledge
4.1.3.	The WFI storage vessel and its components must be fully drainable.	CPP	Product and Process Knowledge
4.1.4.	The WFI storage vessel and its components must be accessible for cleaning and constructed of materials suitable for intended cleaning agents.	CPP	Product and Process Knowledge

4.2. Process Requirements

ID	Requirement	Type	Source
4.2.1.	The WFI storage vessel shall have a working volume ≥ 2,000L.	Business	System Owner
4.2.2.	The WFI storage vessel shall be capable of controlling stored water temperature at set point ± 1°C, within a range of 20°C – 80°C.	Business	System Owner
4.2.3.	The WFI storage vessel shall be capable of self-sanitization, controlling water temperature at ≥ 75°C with recirculation flow rate of ≥ 25 gallons per minute.	Quality	SME
4.2.4.	The WFI storage vessel shall be capable of controlling agitation speed during sanitization at set point ± 5 RPM, within a range of 50 RPM – 300 RPM.	Quality	SME

4.3. Equipment, Design, and Construction Requirements

ID	Requirement	Type	Source
4.3.1.	The WFI storage vessel shall be equipped with a jacket to control stored water temperature.	Business	Company Engineering Standard
4.3.2.	The WFI storage vessel shall be equipped with an	Business	Company

Explicitly define/specify CQAs, CPPs

Type URs based on product quality impact

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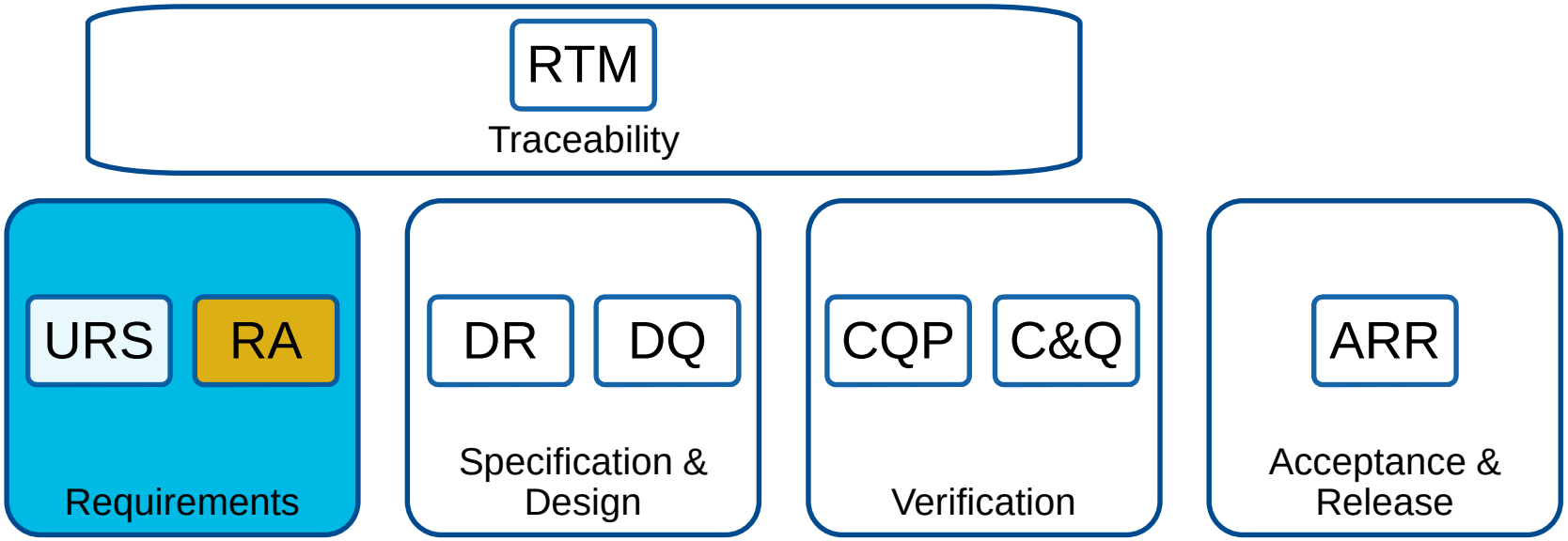
Applying QRM to C&Q Process Deliverables



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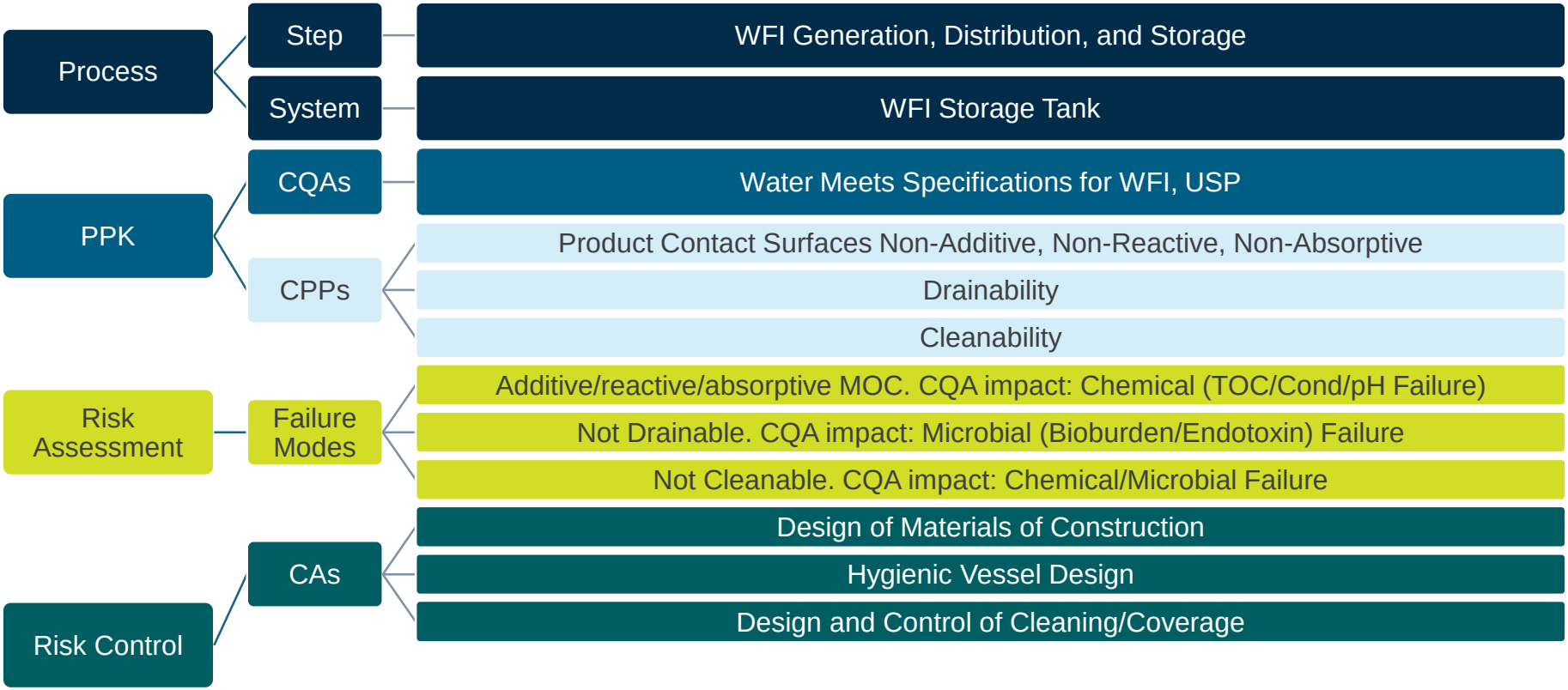

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Applying QRM to C&Q Process Deliverables

Product and Process Knowledge						Baseline System Risk Assessment							
Ref. #	Operations Sequence	Process Description	CQA	CPP	CA	Impact on CQA	How CQA can be Impacted	Design Controls	Recipe Parameters	Associated Alarm	Procedural Controls	Comments	Residual Risk Determination
1	Distribution Loop Return Line	Charges water into the ve from WFI distribution loo supplied by the WFI storag tank.	Water Quality, Chemical	Return Loop Water Conductivity	Control, Monitoring Alarming	Direct	Water TOC, Conductivity, p failure	Inline Conductivity Measurement	N/A	Return Loop Conductivity	Passivation	N/A	Low
			Water Quality, Microbial	Return Loop Water Temperature	Control, Monitoring Alarming	Direct	Water bioburden, endotoxi failure	Return Loop Temperature Sensor	Water storage temperature, 20 - 80°C	Return Loop Temperature	Passivation	N/A	Low
2	Vessel	Provides water	Water Quality	Materials of construction non-additive, non-reactive, non-[illegible]	Design/ Constructio	Direct	Water TOC, Conductivity, p failure	Materials of construction	N/A	N/A	Passivation	N/A	Low
			Water Quality	Materials of construction cleaning	Design/ Constructio	Not Direct	Water TOC, Conductivity, p failure	Materials	N/A	N/A	Passivation	N/A	Low
				Materials of construction suitable for sanitization	Design/ Constructio	Not Direct	Water bioburden, endotoxi failure	Materials of construction	N/A	N/A	N/A	N/A	Low
3	Vessel Bottom/Outlet	Provides outlet for water circulate through the WFI distribution loop.	Water Quality, Microbial	Drainability	Design/ Constructio	Direct	Water bioburden, endotoxi failure	ygienic design (drainability)	N/A	N/A	N/A	N/A	Low
4	Spray Ball	Provides coverage of all wetted surfaces inside the vessel for cleaning	Water Quality, Chemical	Cleanability	Design/ Constructio	Direct	Water TOC, Conductivity, p failure	Hygienic design (spray ball coverage)	N/A	N/A	CIP cycle development	N/A	Low
5	Agitator	Agitates water inside the vessel to ensure homogen temperature during hot w sanitization.	N/A	N/A	N/A	Not Direct	Water bioburden, endotoxi failure	Agitator speed controller, agitator speed indicator	Agitation speed, 50 - 300 RPM	N/A	Agitation required during vessel hot water sanitization	N/A	Low
6	Vessel Jacket	Uses plant steam to contr recirculated water temperature ≥ 75°C durin sanitization.	Water Quality, Microbial	Recirculated Water Temperature	Control, Monitoring Alarming	Not Direct	Water bioburden, endotoxi failure	ssel jacket-controlled water temperature, vessel mperature probes, return loop temperature sensor	Recirculated water temperature, ≥ 75°C, Sanitization time 30 - 120 min	Return Loop Temperature, Vessel Temperature	N/A	N/A	Low
		Uses plant steam and plan chilled water to maintain stored water at setpoint.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Low
7	Plant Steam Supply	Supplied to vessel jacket for stored water temperature control and sanitization.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Low
8	Plant Chilled Water Supply	Supplied to vessel jacket for stored water temperature control.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Low
9	Instrument Air Supply	Supplied to vessel instruments and solenoid valves.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Low
10	Electrical Supply	Supplied to agitator.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Low

CQAs, CPPs, are inputs

Risk Mitigation: Design Controls, Alarms, Procedural Controls

Process Risks to CQAs: Failure to Control CPPs

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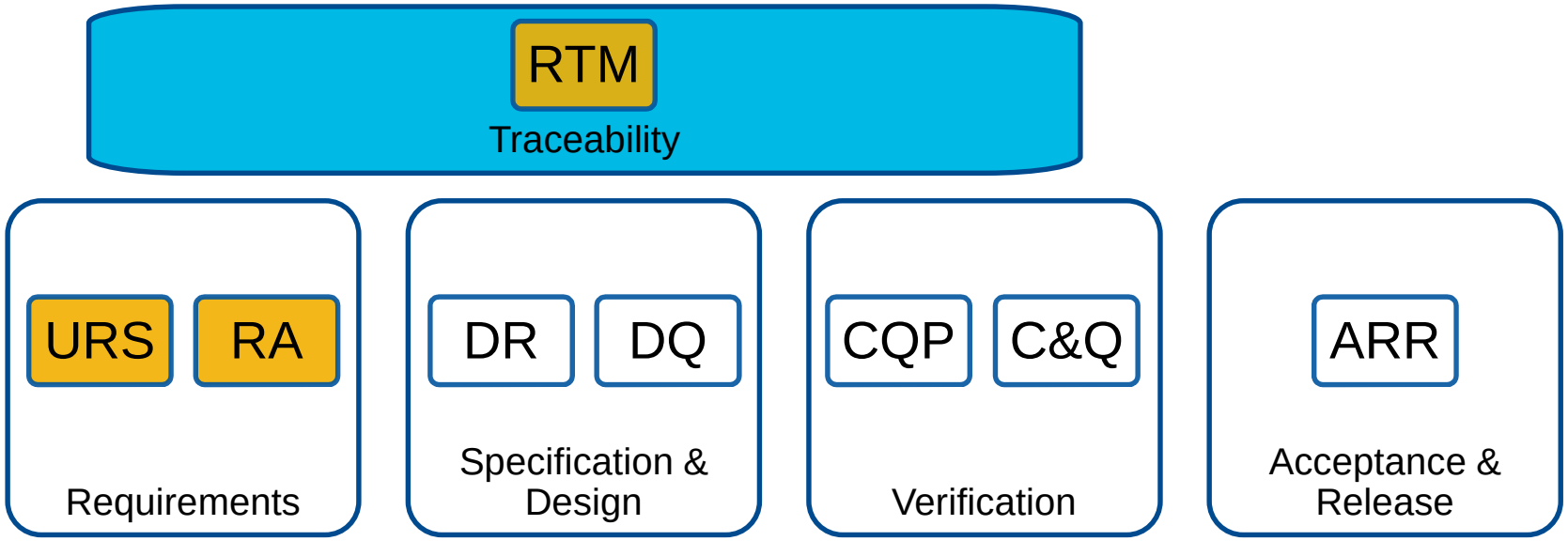
Applying QRM to C&Q Process Deliverables



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Applying QRM to C&Q Process Deliverables

		User Requirement ([Document #])		Risk Assessment ([Document #])					
URS Ref. #	URS Description	Requirement Type	RA Ref. #	Impact	CA	Risk	URS/RA Aligned?	URS/RA Gap Comments
4	**User Requirements**								
4.1	**Critical Quality Requirements and Critical Process Parameters**								
4.1.1	Water stored in the WFI storage vessel shall meet compendial specifications for Water for Injection, USP.	CQA	N/A	N/A	N/A	N/A	N/A	N/A
4.1.2	Surfaces and components that come into contact with WFI must be constructed of materials that are non-additive, non-reactive, and non-absorptive.	CPP	2	Direct	Design/ Construction	Low	Yes	N/A
4.1.3	The WFI storage vessel and its components must be fully drainable.	CPP	3	Direct	Design/ Construction	Low	Yes	N/A
4.1.4	The WFI storage vessel and its components must be accessible for cleaning and constructed of materials suitable for intended cleaning agents.	CPP	4	Direct	Design/ Construction	Low	Yes	N/A
3.2	**Process Requirements**								
4.2.1	The WFI storage vessel shall have a working volume ≥ 2,000L.	Business	N/A	N/A	N/A	N/A	Yes	N/A
4.2.2	The WFI storage vessel shall be capable of controlling stored water temperature at set point ± 1°C, within a range of 20°C – 80°C.	Business	7	N/A	N/A	N/A	Yes	N/A
4.2.3	The WFI storage vessel shall be capable of self-sanitization, controlling water temperature at 75°C with recirculation flow rate of ≥ 25 gallons per minute.	Quality	7	Not Direct	N/A	N/A	Yes	N/A
4.2.4	The WFI storage vessel shall be capable of controlling agitation speed during sanitization at t point ± 5 RPM, within a range of 50 RPM – 300 RPM.	Quality	6	Not Direct	N/A	N/A	Yes	N/A
4.3	**Equipment, Design, and Construction Requirements**								
4.3.1	The WFI storage vessel shall be equipped with a jacket to control stored water temperature.	Business	6	N/A	N/A	N/A	Yes	N/A
4.3.2	The WFI storage vessel shall be equipped with an agitator.	Business	5	N/A	N/A	N/A	Yes	N/A
4.3.3	The WFI storage vessel shall be supplied with one or more [illegible]	Business	[illegible]	[illegible]	[illegible]	[illegible]	Yes	N/A
4.3.4	The WFI storage vessel and its components must be accessible for sanitization and constructed of materials suitable for sanitization.	Quality	2	Not Direct	N/A	N/A	Yes	N/A

URS -> Risk Assessment

Risk Controls (CAs) trace to CQAs, CPPs

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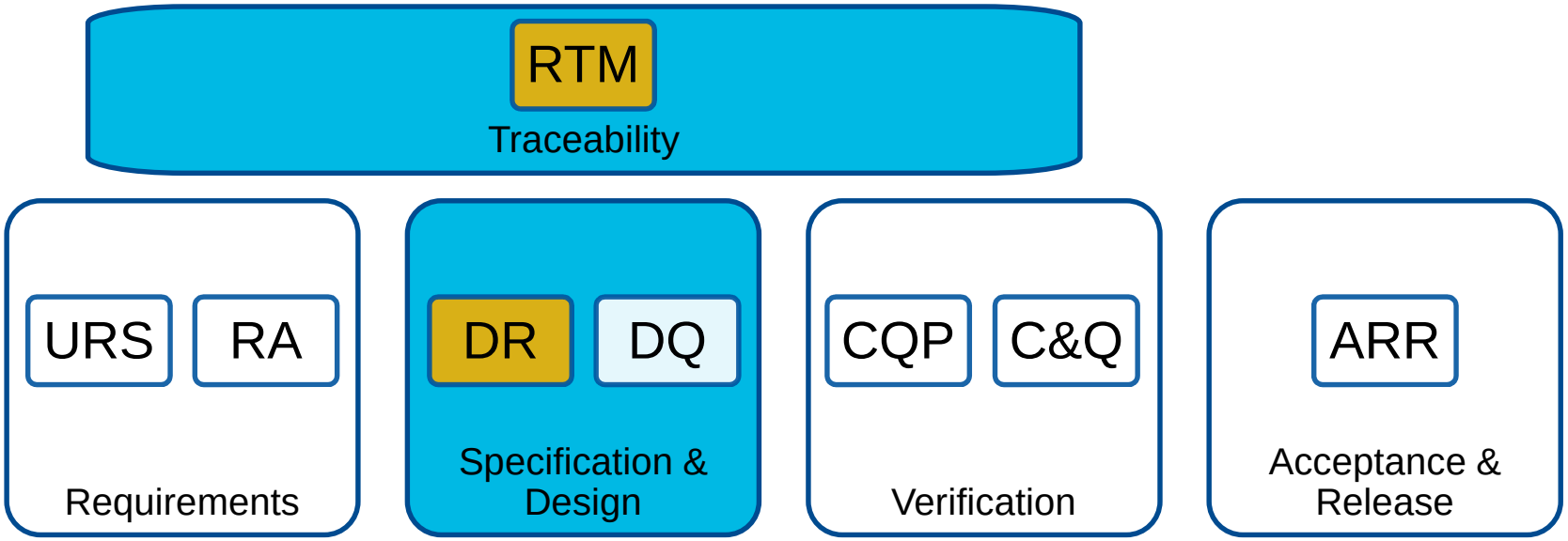
Applying QRM to C&Q Process Deliverables



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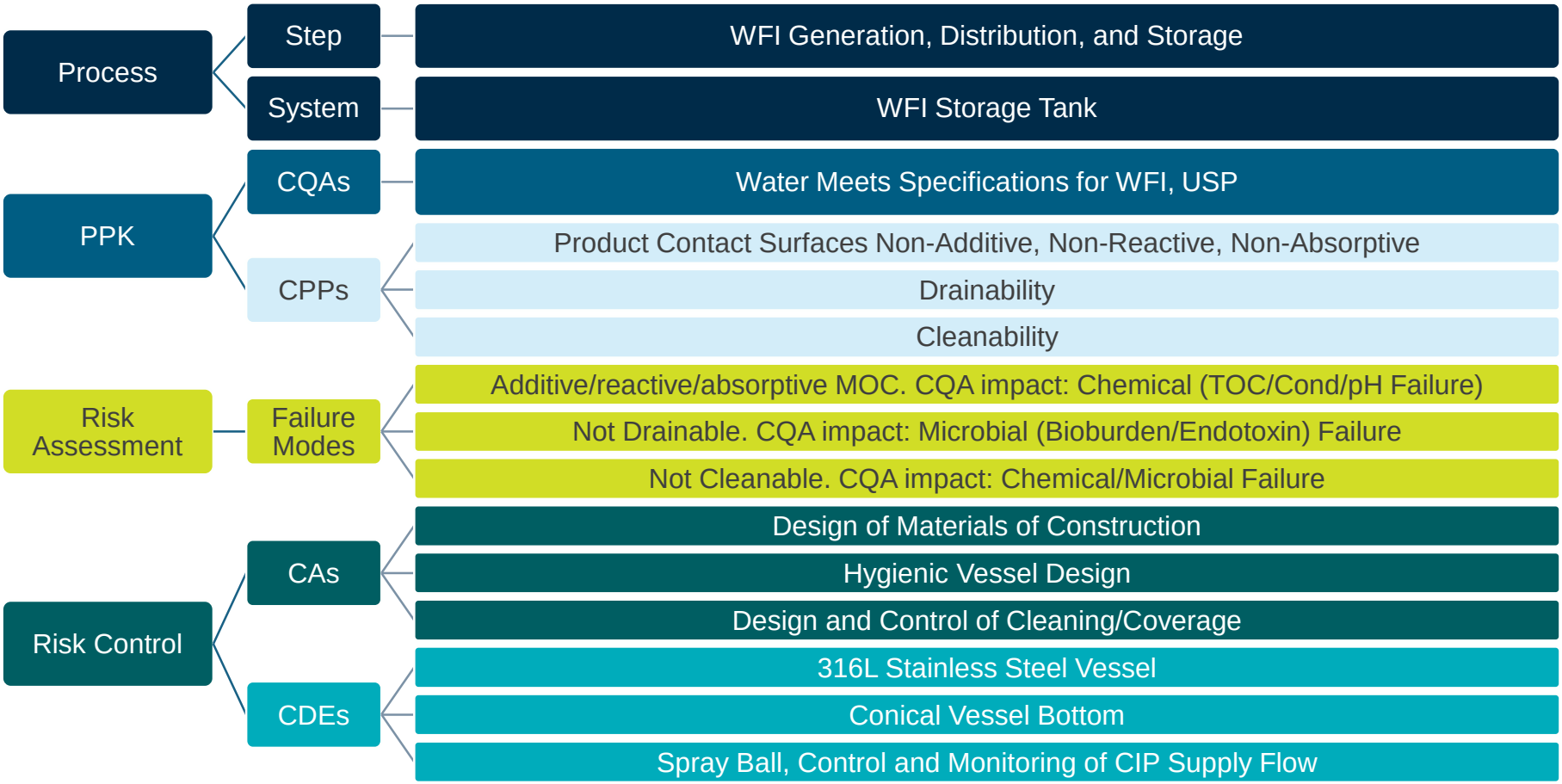

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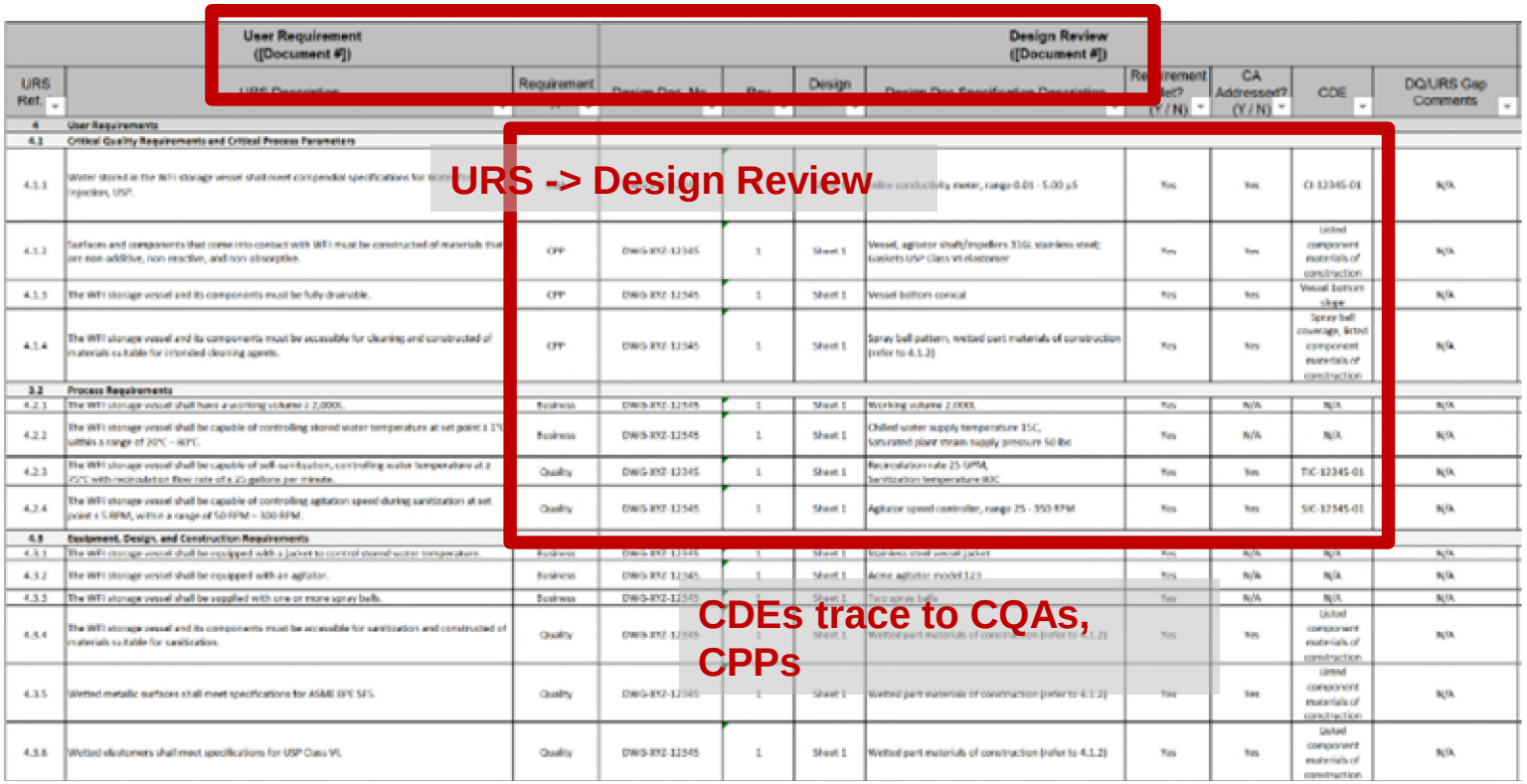

	User Requirement ([Document #])		Design Review ([Document #])							
URS Ref.	URS Description	Requirement	Design Doc. No.	Rev.	Design	Design Doc Specification Description	Requirement Met? (Y / N)	CA Addressed? (Y / N)	CDE	DQ/URS Gap Comments
4	**User Requirements**									
4.1	**Critical Quality Requirements and Critical Process Parameters**									
4.1.1	Water stored in the WFI storage vessel shall meet compendial specifications for water for injection, USP.	CPP	DWG-XYZ-12345	1	Sheet 1	Inline conductivity meter, range 0.01 - 5.00 µS	Yes	Yes	CI-12345-01	N/A
4.1.2	Surfaces and components that come into contact with WFI must be constructed of materials that are non-additive, non-reactive, and non-absorptive.	CPP	DWG-XYZ-12345	1	Sheet 1	Vessel, agitator shaft/impellers 316L stainless steel; Gaskets USP Class VI elastomer	Yes	Yes	Listed component materials of construction	N/A
4.1.3	The WFI storage vessel and its components must be fully drainable.	CPP	DWG-XYZ-12345	1	Sheet 1	Vessel bottom conical	Yes	Yes	Vessel bottom shape	N/A
4.1.4	The WFI storage vessel and its components must be accessible for cleaning and constructed of materials suitable for intended cleaning agents.	CPP	DWG-XYZ-12345	1	Sheet 1	Spray ball pattern, wetted part materials of construction (refer to 4.1.2)	Yes	Yes	Spray ball coverage, listed component materials of construction	N/A
3.2	**Process Requirements**									
4.2.1	The WFI storage vessel shall have a working volume ≥ 2,000L.	Business	DWG-XYZ-12345	1	Sheet 1	Working volume 2,000L	Yes	N/A	N/A	N/A
4.2.2	The WFI storage vessel shall be capable of controlling stored water temperature at set point ± 1°C within a range of 70°C – 80°C.	Business	DWG-XYZ-12345	1	Sheet 1	Chilled water supply temperature 1°C, Saturated plant steam supply pressure 50 lbs	Yes	N/A	N/A	N/A
4.2.3	The WFI storage vessel shall be capable of self-sanitization, controlling water temperature at ≥ 121°C with recirculation flow rate of ≥ 25 gallons per minute.	Quality	DWG-XYZ-12345	1	Sheet 1	Recirculation rate 25 GPM, Sanitization temperature 80C	Yes	Yes	TIC-12345-01	N/A
4.2.4	The WFI storage vessel shall be capable of controlling agitation speed during sanitization at set point ± 5 RPM, within a range of 50 RPM – 300 RPM.	Quality	DWG-XYZ-12345	1	Sheet 1	Agitator speed controller, range 25 - 350 RPM	Yes	Yes	SIC-12345-01	N/A
4.3	**Equipment, Design, and Construction Requirements**									
4.3.1	The WFI storage vessel shall be equipped with a jacket to control stored water temperature.	Business	DWG-XYZ-12345	1	Sheet 1	Stainless steel vessel jacket	Yes	N/A	N/A	N/A
4.3.2	The WFI storage vessel shall be equipped with an agitator.	Business	DWG-XYZ-12345	1	Sheet 1	Acme agitator model 123	Yes	N/A	N/A	N/A
4.3.3	The WFI storage vessel shall be supplied with one or more spray balls.	Business	DWG-XYZ-12345	1	Sheet 1	Two spray balls	Yes	N/A	N/A	N/A
4.3.4	The WFI storage vessel and its components must be accessible for sanitization and constructed of materials suitable for sanitization.	Quality	DWG-XYZ-12345	1	Sheet 1	Wetted part materials of construction (refer to 4.1.2)	Yes	Yes	Listed component materials of construction	N/A
4.3.5	Wetted metallic surfaces shall meet specifications for ASME BPE SF5.	Quality	DWG-XYZ-12345	1	Sheet 1	Wetted part materials of construction (refer to 4.1.2)	Yes	Yes	Listed component materials of construction	N/A
4.3.6	Wetted elastomers shall meet specifications for USP Class VI.	Quality	DWG-XYZ-12345	1	Sheet 1	Wetted part materials of construction (refer to 4.1.2)	Yes	Yes	Listed component materials of construction	N/A

URS -> Design Review

CDEs trace to CQAs, CPPs

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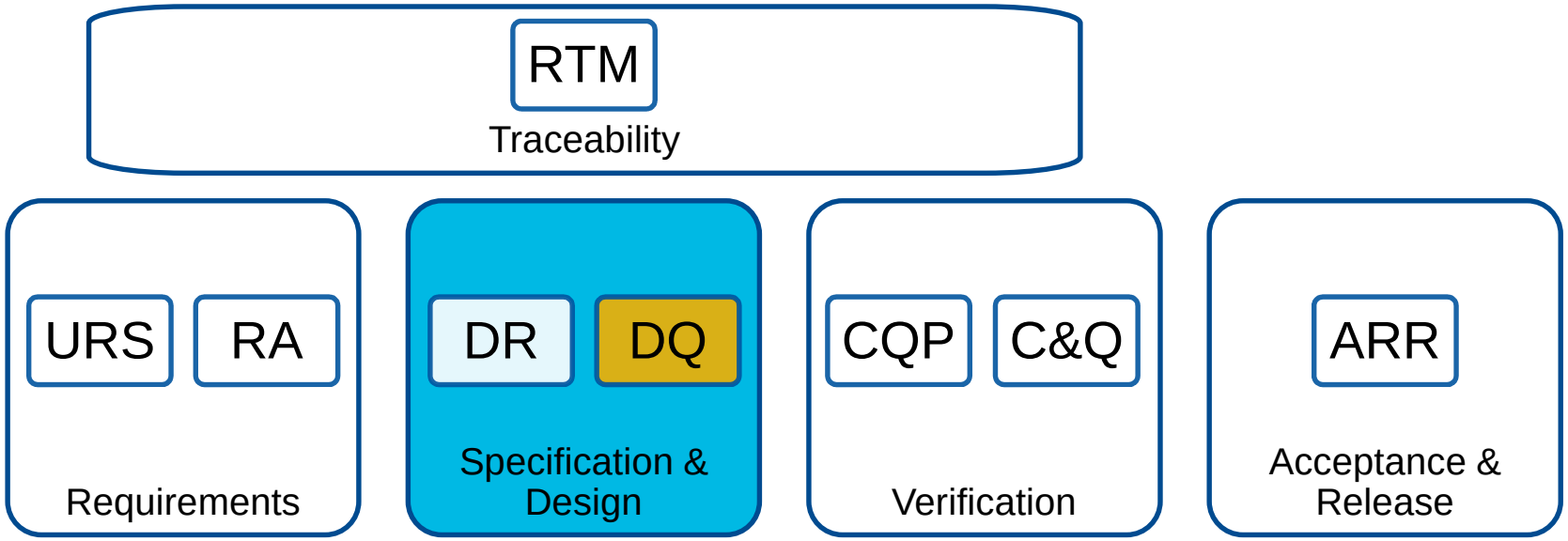

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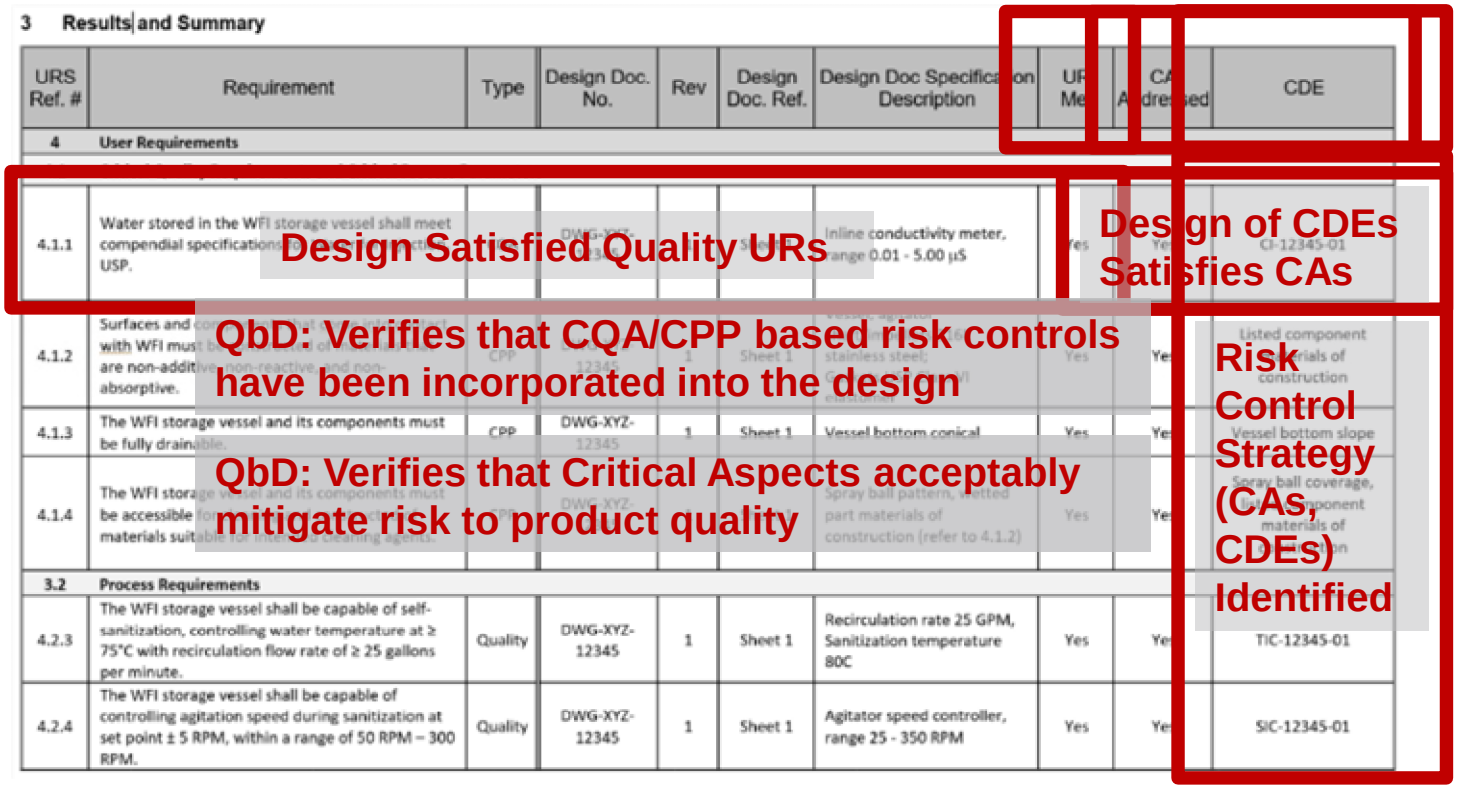

3 Results and Summary

URS Ref. #	Requirement	Type	Design Doc. No.	Rev	Design Doc. Ref.	Design Doc Specification Description	UR Met	CA Addressed	CDE
4	**User Requirements**								
4.1.1	Water stored in the WFI storage vessel shall meet compendial specifications USP.					Inline conductivity meter, range 0.01 - 5.00 µS	Yes	Yes	CI-12345-01
4.1.2	Surfaces and components that come in contact with WFI must be [illegible] are non-additive, non-reactive, and non-absorptive.	CPP	DWG-XYZ-12345	1	Sheet 1	[illegible] stainless steel	Yes	Yes	Listed component materials of construction
4.1.3	The WFI storage vessel and its components must be fully drainable.	CPP	DWG-XYZ-12345	1	Sheet 1	Vessel bottom conical	Yes	Yes	Vessel bottom slope
4.1.4	The WFI storage vessel and its components must be accessible for [illegible] materials suitable for [illegible] cleaning agents.	CPP	DWG-XYZ-12345	1	Sheet 1	Spray ball pattern, wetted part materials of construction (refer to 4.1.2)	Yes	Yes	Spray ball coverage, Component materials of construction
3.2	**Process Requirements**								
4.2.3	The WFI storage vessel shall be capable of self-sanitization, controlling water temperature at ≥ 75°C with recirculation flow rate of ≥ 25 gallons per minute.	Quality	DWG-XYZ-12345	1	Sheet 1	Recirculation rate 25 GPM, Sanitization temperature 80C	Yes	Yes	TIC-12345-01
4.2.4	The WFI storage vessel shall be capable of controlling agitation speed during sanitization at set point ± 5 RPM, within a range of 50 RPM – 300 RPM.	Quality	DWG-XYZ-12345	1	Sheet 1	Agitator speed controller, range 25 - 350 RPM	Yes	Yes	SIC-12345-01

Design Satisfied Quality URs

Design of CDEs Satisfies CAs

QbD: Verifies that CQA/CPP based risk controls have been incorporated into the design

Risk Control Strategy (CAs, CDEs) Identified

QbD: Verifies that Critical Aspects acceptably mitigate risk to product quality

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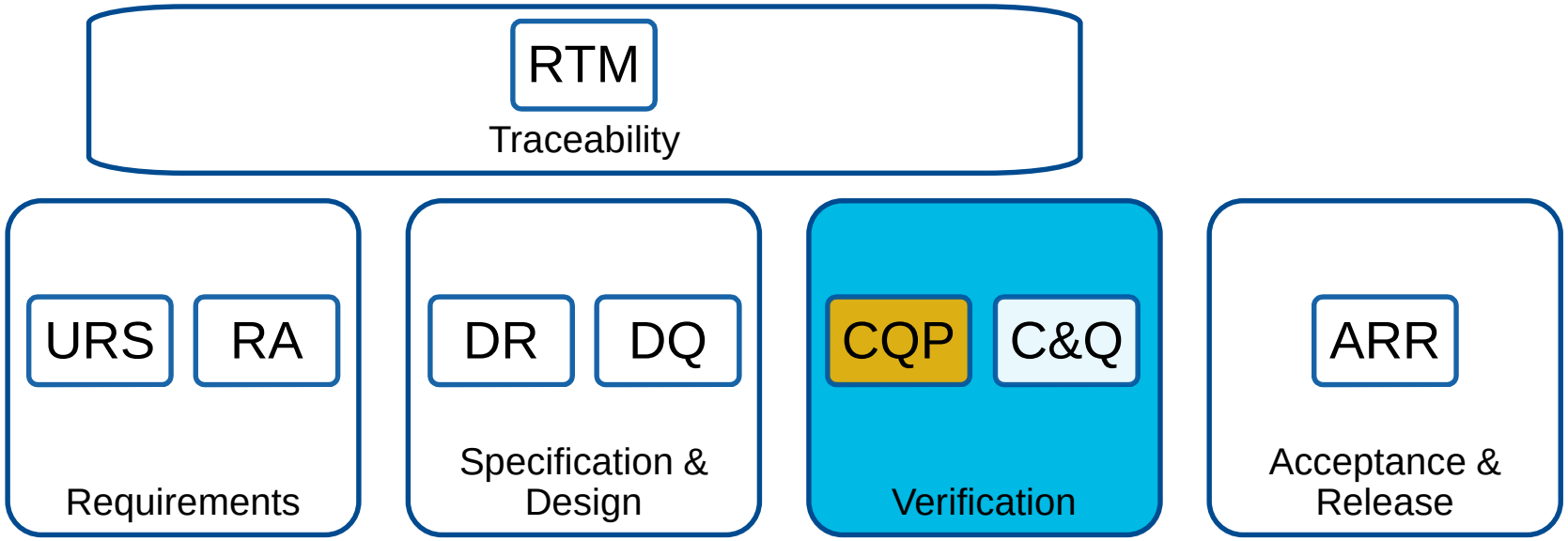

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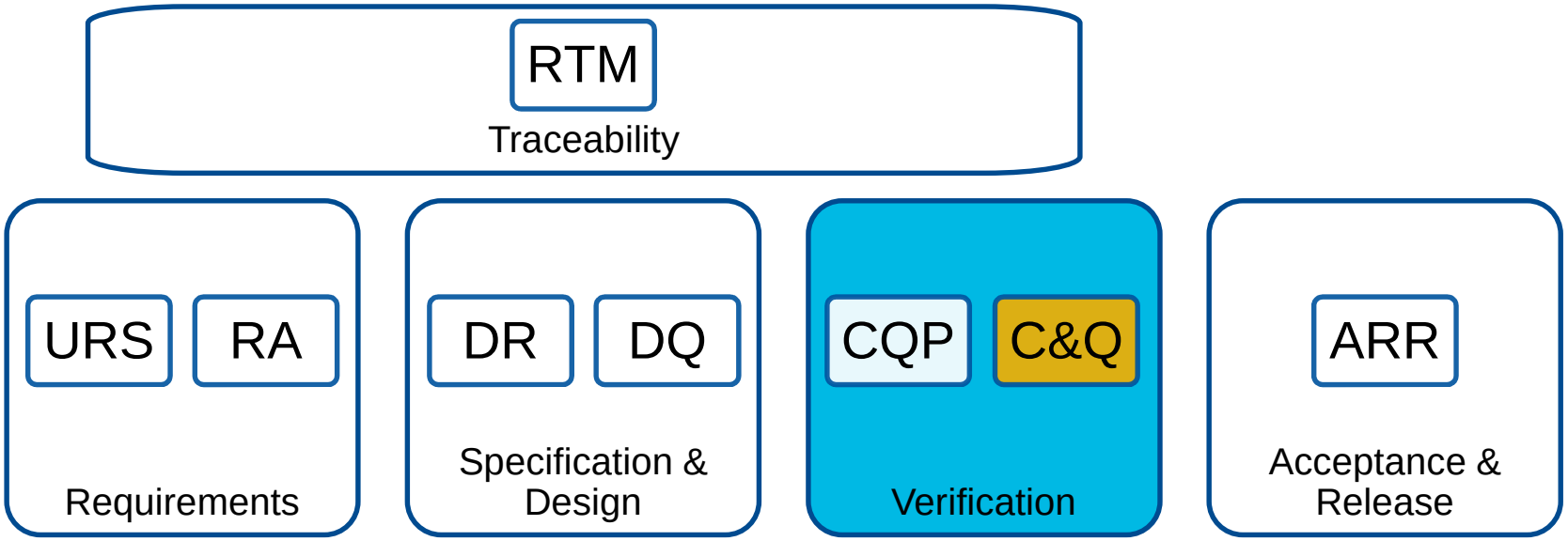

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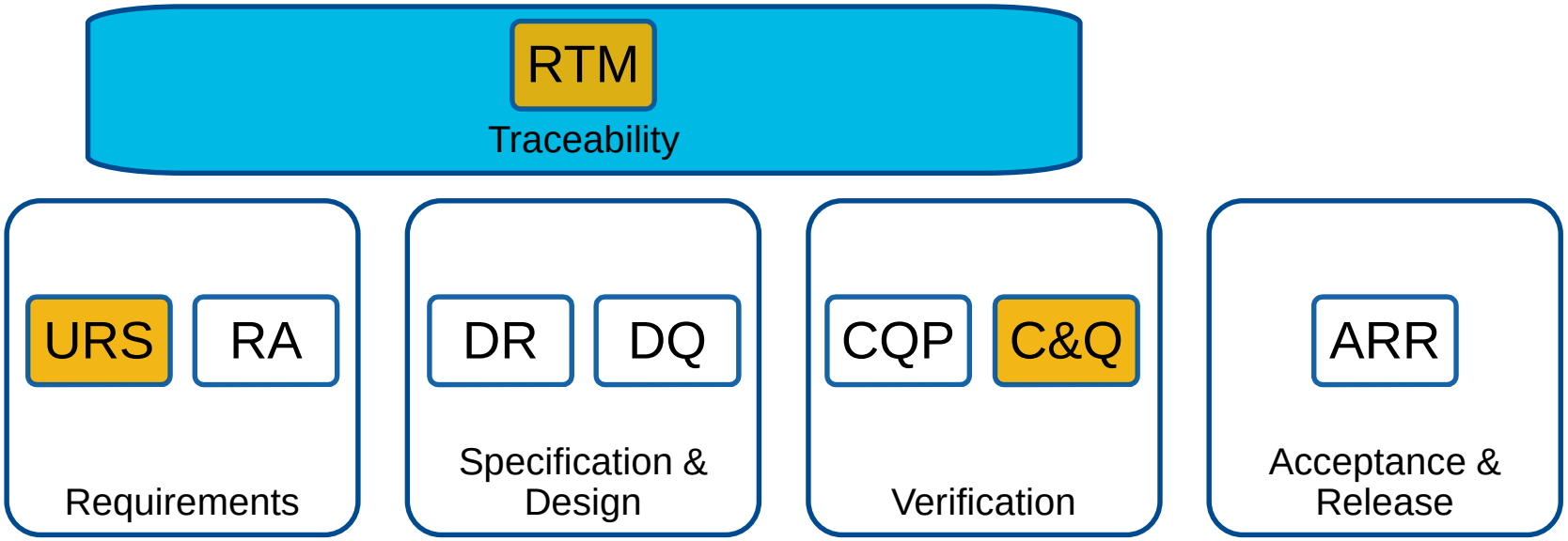

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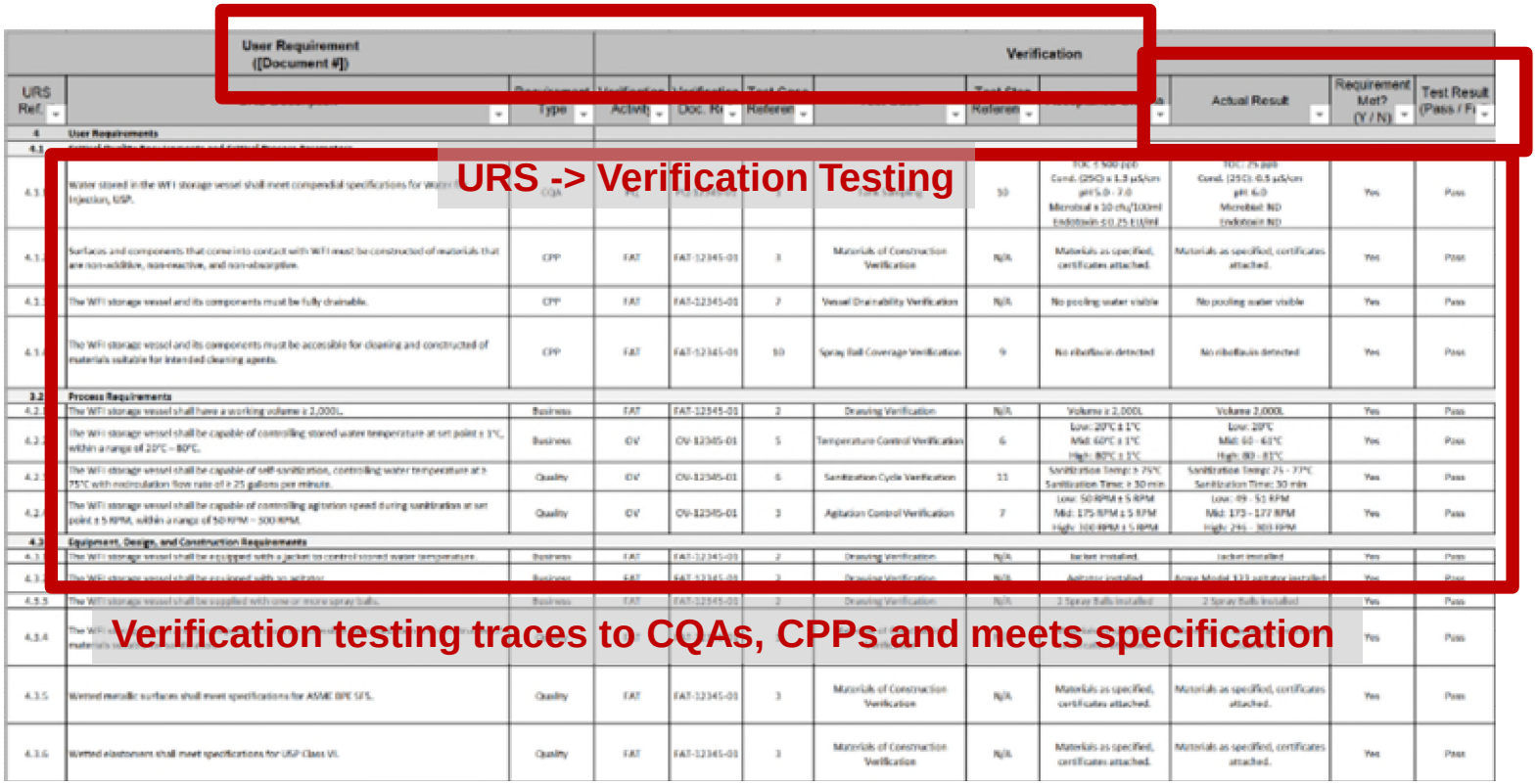

	User Requirement ([Document #])		Verification							
URS Ref.		Type	Activity	Doc. Ref.	Test Case Reference		Test Step Reference		Actual Result	Requirement Met? (Y / N)	Test Result (Pass / Fail)
4	**User Requirements**										
4.1											
4.1.1	Water stored in the WFI storage vessel shall meet compendial specifications for water for Injection, USP.	CQA	IV	IV-12345-01	10	Water Quality Verification	10	TOC: < 500 ppb Cond. (25C): ≤ 1.3 µS/cm pH: 5.0 - 7.0 Microbial: ≤ 10 cfu/100ml Endotoxin: ≤ 0.25 EU/ml	TOC: 25 ppb Cond. (25C): 0.5 µS/cm pH: 6.0 Microbial: ND Endotoxin: ND	Yes	Pass
4.1.2	Surfaces and components that come into contact with WFI must be constructed of materials that are non-additive, non-reactive, and non-absorptive.	CPP	FAT	FAT-12345-01	3	Materials of Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass
4.1.3	The WFI storage vessel and its components must be fully drainable.	CPP	FAT	FAT-12345-01	7	Vessel Drainability Verification	N/A	No pooling water visible	No pooling water visible	Yes	Pass
4.1.4	The WFI storage vessel and its components must be accessible for cleaning and constructed of materials suitable for intended cleaning agents.	CPP	FAT	FAT-12345-01	10	Spray Ball Coverage Verification	9	No riboflavin detected	No riboflavin detected	Yes	Pass
3.2	**Process Requirements**										
4.2.1	The WFI storage vessel shall have a working volume ≥ 2,000L.	Business	FAT	FAT-12345-01	2	Drawing Verification	N/A	Volume ≥ 2,000L	Volume 2,000L	Yes	Pass
4.2.2	The WFI storage vessel shall be capable of controlling stored water temperature at set point ± 1°C, within a range of 20°C – 80°C.	Business	OV	OV-12345-01	5	Temperature Control Verification	6	Low: 20°C ± 1°C Mid: 60°C ± 1°C High: 80°C ± 1°C	Low: 20°C Mid: 60 - 61°C High: 80 - 81°C	Yes	Pass
4.2.3	The WFI storage vessel shall be capable of self-sanitization, controlling water temperature at ≥ 75°C with recirculation flow rate of ≥ 25 gallons per minute.	Quality	OV	OV-12345-01	6	Sanitization Cycle Verification	11	Sanitization Temp: ≥ 75°C Sanitization Time: ≥ 30 min	Sanitization Temp: 75 - 77°C Sanitization Time: 30 min	Yes	Pass
4.2.4	The WFI storage vessel shall be capable of controlling agitation speed during sanitization at set point ± 5 RPM, within a range of 50 RPM – 500 RPM.	Quality	OV	OV-12345-01	3	Agitation Control Verification	7	Low: 50 RPM ± 5 RPM Mid: 175 RPM ± 5 RPM High: 300 RPM ± 5 RPM	Low: 49 - 51 RPM Mid: 173 - 177 RPM High: 295 - 303 RPM	Yes	Pass
4.3	**Equipment, Design, and Construction Requirements**										
4.3.1	The WFI storage vessel shall be equipped with a jacket to control stored water temperature.	Business	FAT	FAT-12345-01	2	Drawing Verification	N/A	Jacket installed	Jacket installed	Yes	Pass
4.3.2	The WFI storage vessel shall be equipped with an agitator.	Business	FAT	FAT-12345-01	2	Drawing Verification	N/A	Agitator installed	Arrow Model 333 agitator installed	Yes	Pass
4.3.3	The WFI storage vessel shall be supplied with one or more spray balls.	Business	FAT	FAT-12345-01	2	Drawing Verification	N/A	2 Spray Balls installed	2 Spray Balls installed	Yes	Pass
4.3.4	The WFI [illegible] materials [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	Yes	Pass
4.3.5	Wetted metallic surfaces shall meet specifications for ASME BPE SF5.	Quality	FAT	FAT-12345-01	3	Materials of Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass
4.3.6	Wetted elastomers shall meet specifications for USP Class VI.	Quality	FAT	FAT-12345-01	3	Materials of Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass

URS -> Verification Testing

Verification testing traces to CQAs, CPPs and meets specification

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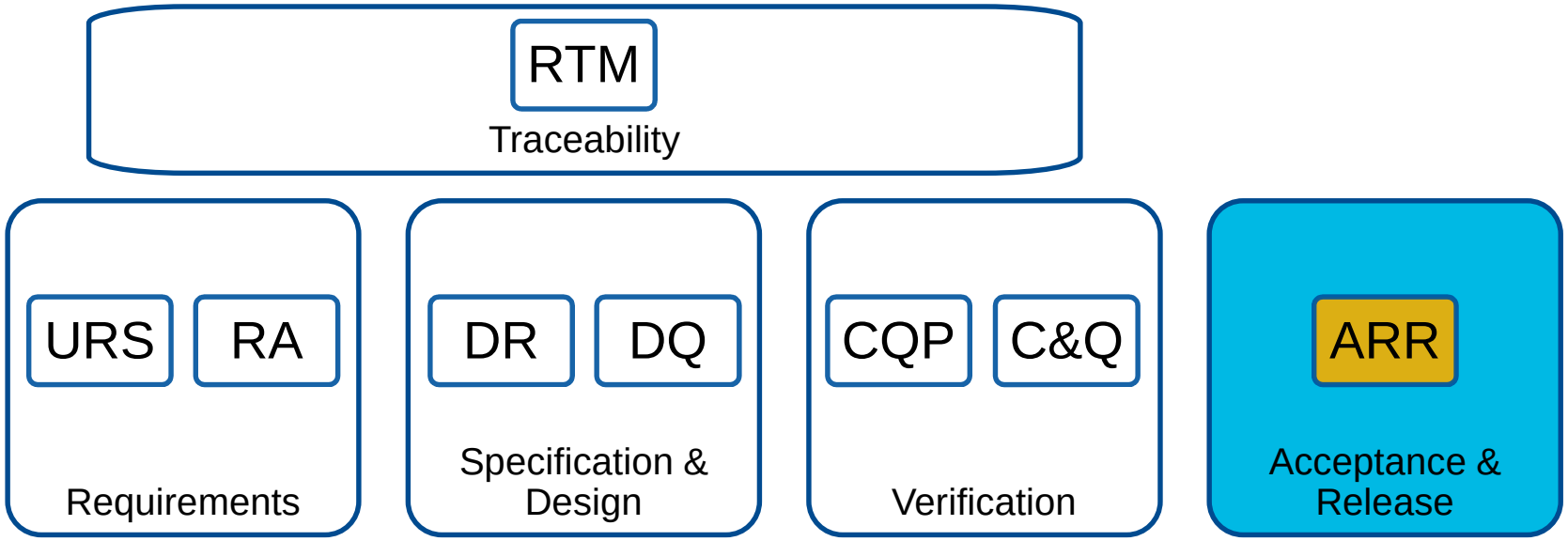

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Applying QRM to C&Q Process Deliverables

Title: IOQ Summary Report <Insert System Name> System

Document ID: <Insert Doc #>

Revision: 00

URS Ref.	Requirement	Type	CA	CDE	C	Doc. Ref.	Test Case Ref	Test Case	Test Step	Acceptance Criteria	Actual Result	Req. Met	Test Result
3.2	**Process Requirements**												
4.2.3	The WFI storage vessel self-sanitization, controlling water temperature at ≥ 75°C with recirculation flow [illegible]	Quality	[illegible]	[illegible]		[illegible]345-01	6	Sanitization Cycle Verification	11	Sanitization Temp: ≥ 75°C Sanitization Time: ≥ 30 min	Sanitization Temp: 75 - 77°C Sanitization Time: 30 min	Yes	Pass
4.2.4	The WFI storage vessel shall be capable of controlling [illegible] speed for sanitization at set point ± 5 RPM, within a range of 50 RPM – 300 RPM.	Quality	[illegible]	[illegible]		[illegible]345-01	4	Control Verification	7	Low: 50 RPM ± 5 RPM Mid: 175 RPM ± 5 RPM High: 300 RPM ± 5 RPM	Low: 50 - 53 RPM Mid: 171 - 177 RPM High: 296 - 303 RPM	Yes	Pass
4.3	**Equipment, Design, and Construction Requirements**												
4.3.4	The WFI storage vessel and its components shall be capable of sanitization and constructed of materials suitable for sanitization.	Quality	N/A	Listed component materials of construction		FAT-12345-01	3	Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass
4.3.5	Wetted metallic surfaces shall meet specifications for ASME BPE SFS.	Quality	Design/ Construction	Listed component materials of construction		FAT-12345-01	3	Materials of Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass
4.3.6	Wetted elastomers shall meet specifications for USP Class VI.	Quality	Design/ Construction	Listed component materials of construction		FAT-12345-01	3	Materials of Construction Verification	N/A	Materials as specified, certificates attached.	Materials as specified, certificates attached.	Yes	Pass

System Satisfies Critical Aspects (CA)

Installation and Operation of CDEs are fit for intended use

System Meets Specification for Quality URs

Benefits/Opportunities

Benefits and opportunities from ISPE Baseline Guide Volume 5, 2nd Ed.

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Benefits of Changes to C&Q Processes

Process	Historical Approach	Apply	New Approach	Benefit
C&Q Testing	**Qualification** protocols **at** project **end** with testing redundant to engineering lifecycle	**Good Engineering Practices**	**Qualification** process **integrated** into engineering project without non-value-added redundant testing	Efficient use of **resources** and reduced pressure on project **schedule**
Requirements	**Qualification** testing **based on** equipment **specifications** and capabilities	**Quality Risk Management**	**Testing** considers **controls**, **detection** mechanisms, and all quality systems	**Focuses** qualification **efforts** on defined **critical aspects**
Design	**Design review** applied **inconsistently** with **unstructured** Quality involvement	**Systematic Design Review**	**Design review well-directed** with defined Quality involvement	**Enables** appropriate and defendable **Quality oversight**
Change Management	**Changes** are **not well-controlled** until a system is qualified and released for use	**Engineering Change Management**	All **changes** are effectively **managed throughout** the engineering project	**Prevents** the need to perform **redundant testing** at project end

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Applying QRM Through the System Lifecycle

Process Development	Define Product/Process Knowledge (PPK): CQA, CPP
Risk Assessment	Identify Risks to Product Quality
Risk Control	Identify Critical Aspects (CAs) to Mitigate Identified Risks
Risk Review	Design Review: Identify CDEs / Risk Control Strategy
Quality by Design (QbD)	Design Qualification: Design of Risk Controls (CAs/CDEs) Acceptably Mitigates Risk
C&Q Strategy	Verify CAs/CDEs, Testing Rigor Commensurate w/Risk
Risk Review	Periodic Review/Revalidation, Continuous Improvement, Change Management, Deviation/CAPA Management

Discussion

Questions?

For further information, please contact
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CAI
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Supporting Processes

Supporting processes and enablers for the QRM-based integrated C&Q process

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System Risk Assessment

Central to Integrated C&Q Approach:

- **Defines risk to product quality**
- **Identifies Risk Controls**
- **Determines instrument/alarm criticality**
- **Links verification activities to process and product quality controls**
- **Provides rationale for C&Q strategy**

Benefits of System Risk Assessment:

- **Provides focal point for Design Review and Design Qualification**
- **Defines control strategy for process risks, focuses Quality on product quality/CDEs**
- **Provides a focus for C&Q to ensure controls are in place and tested**
- **Established traceability from Qualification Summary to lifecycle activities and verification**

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Supporting Processes: System Classification

High-level first pass to identify systems with direct product quality impact

Based on system boundaries for integrated testing

Same yes-no question methodology, updated questions

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?

Supporting Processes: Good Engineering Practice (GEP)

Design Review:

- **Ensures design meets URS**
- **Identifies CDEs that satisfy Critical Aspects**
- **Supports implementation of Quality by Design (QbD) principles**
- **Culminates in DQ**

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Supporting Processes: Good Engineering Practice (GEP)

Engineering Change Management:

- **System lifecycle process: Design through Operation to End of Life**
- **Following final design acceptance, subsequent changes evaluated for quality impact**
  - CQA, CPP, CA, CDE
- **Project ECM through C&Q**
- **After system acceptance and release:**
  - Site ECM
  - Quality Change Control if quality impact

Supporting Processes: Good Engineering Practice (GEP)

Engineering Quality Process:

- **Documented activities during system lifecycle stages:**
  - Design/Procurement: Vendor/Supplier Management
  - Implementation: Construction Quality, Commissioning, Handover
  - Operations: Asset Management, Calibration, Maintenance
- **Supporting systems throughout system lifecycle:**
  - Document/Drawing Control
  - Issue/Punchlist Management
  - Engineering Good Documentation Practice (GDP)