Development of a Quality Management System

For Laboratory Developed Tests

How to Guide

Let’s get started and learn the steps to develop a regulatory quality management system!

This Quality Management System “How to Guide” can be found in its entirety within the following dissertation: D'Angelo, Rita, "An Agile Quality Management System for Laboratory Developed Tests" (2018). *Wayne State University Dissertations*. 1920. https://digitalcommons.wayne.edu/oa_dissertations/1920

01 Introduction

Development of a Quality Management System

This step-by-step instruction will assist the learner assess the regulatory needs of the laboratory and will illustrate gaps in the process. This guide outlines the steps for development of policies, procedures and processes to implement a robust quality management system framework that will comply with all pertinent regulations. This guide includes a description of each phase within seven phases of development. Sequential steps are outlined throughout the document that correlate with the tabs on the excel workbook. This workbook provides the opportunity to actively develop the steps as learners move through the course. The conclusion of each phase include an action item reminder of the deliverables. This reminder prompts the reader by highlighting the importance of the discussion and illustrates further instruction.

The framework depicted in Figure 1. Consists of the following seven phases of development:

Phase I: Development of a Leadership Support Structure

Phase II: Training

Phase III: Pre-Assessment of existing processes

Phase IV: Development of a Quality Management System

Phase V: Process Controls

Phase VI: Process validation plan and protocol to ensure the framework is operating as intended

Phase VII: Development of a Quality Management System

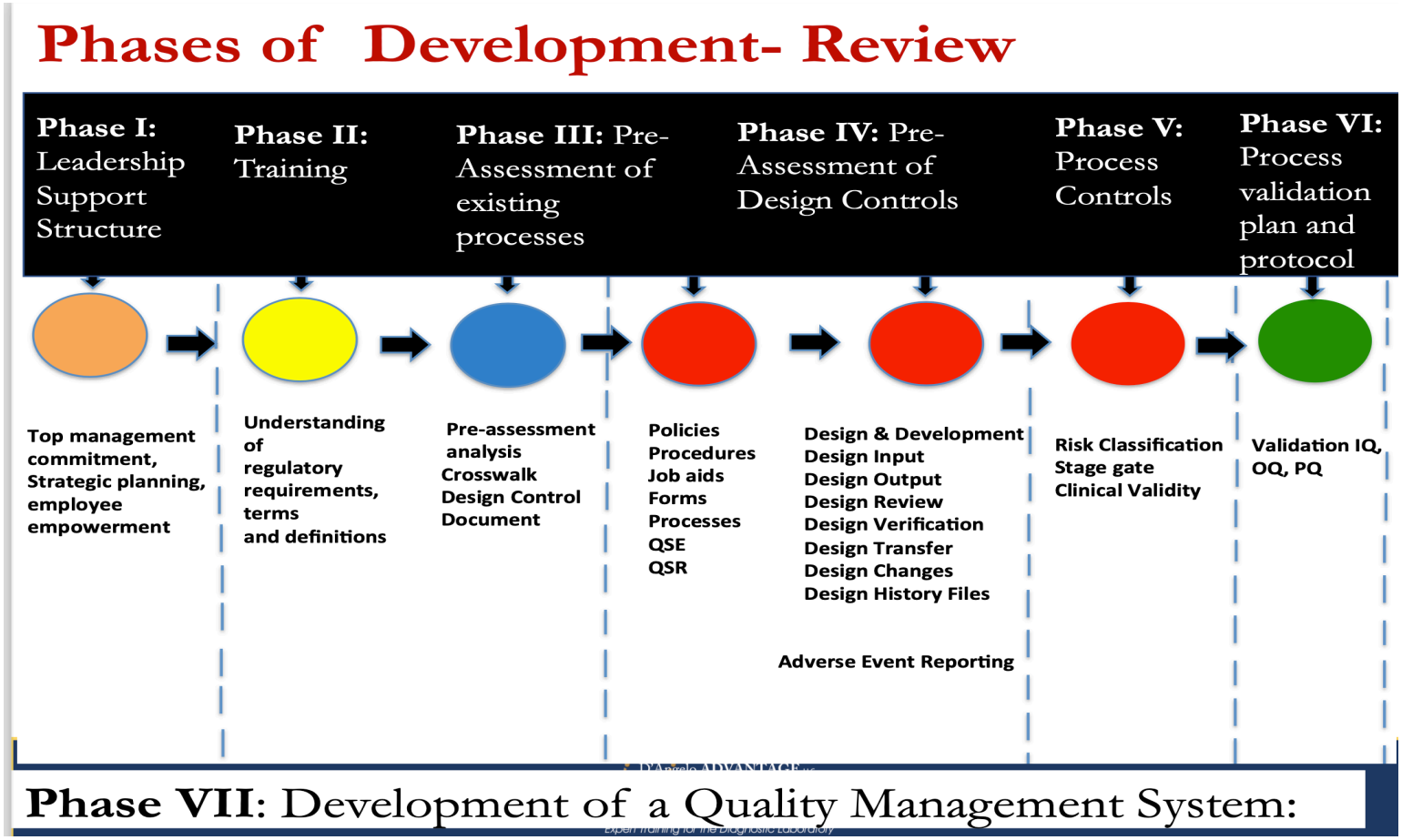


Figure 1. QMS Phases of Development

Phase I Leadership Support

The first phase in the development of a quality management system include a leadership support structure. This support structure directs the organization in quality, oversees the development of processes, policies and procedures, removes any obstacles within the path of change and provides the necessary resources. Leadership commitment is key to ensure a quality structure will sustain the initiative and provide ongoing support.

Leadership commitments include the following:

1. Development of a regulatory strategic plan
2. Key performance indicators to outline and measure regulatory initiatives
    - Leadership participation, sponsorship, directives and support
3. The assignment of roles and responsibilities to every aspect of the QMS framework:
    - The establishment of a QMS includes oversight by a knowledgeable, educated, responsible, informed, cohesive team to effectively manage the process
4. Establishment of an LDT quality committee to quickly approve changes and provide support
5. Establish a formal structure to communicate change throughout the organization

Phase I Leadership Action Items

	LEADERSHIP ACTION ITEMS: List the following:	Complete
1.	Provide leadership support for creating an LDT structure	
2.	Establish communication pathways to ensure continuous communication throughout the process	
3	Form an LDT Oversight Team	
	a. Leader	
	b. Team	

Instructions:

1. Assign leaders, team leads, and accountable persons to serve the process
2. Develop a formal communication process to focus on the importance of change

Module 2. Form 2

Action Item

Identify subject matter experts to educate, serve as mentors and oversee the entire developmental process

Phase II Training

The training program includes a description of regulatory requirements, translation of terms and definitions to laboratory understanding and highlights the importance of documentation throughout the process.

The program includes training modules for the following:

1. **What's My Role?**

    a. Introduction to the manufacture of Laboratory Developed Tests and roles and responsibility of leaders and staff

2. **Understanding regulatory guidelines**

    a. Regulatory requirements, terms and definitions in alignment with CLIA 88, 12 QSE, 21 CFR 820/QSR and Design Control

3. **Stage Gate Process: From Idea to Test Environment**

    a. The program includes demonstration of the LDT process beginning with research and development and ending with diagnostic testing. The process includes handoffs, tasks, activities and all aspects of development through the gates that include go/no go.

Phase II Training

	TRAINING ACTION ITEMS: List the following:				
		Complete			
1	Identify subject matter experts to serve as trainers				
2	Identify LDT team members who require training				
3	List all pertinent organizational guidance documents, regulations and specific requirements to be included in training				
	a. 21 CFR 820				
4	Develop training modules				
5	Schedule training				

Instructions:

Provide education for leaders and change agents to manage and oversee each developmental step. Include a standard review: 21 CFR, QSE and CLIA regulations.

Module 2 Form 3

Action Item

Identify team members and provide training for all roles within LDT development

Crosswalk I: QSE in Comparison to Your Laboratory Processes

The pre-assessment phase includes a preliminary review or a gap analysis of the current quality management structure that include policies, procedures and processes that currently resides within the laboratory.

Many laboratories have adopted the CLSI quality management guidance from CLIA 88 requirements and CFR 493 translated to the 12 Quality System Essentials (QSE) and exist within laboratories today.

In addition, many laboratories have also adopted quality management standards, such as ISO 9001 or 15189, 17025 that better prepare the laboratory for adherence to regulatory requirements.

Phase III Pre-Assessment

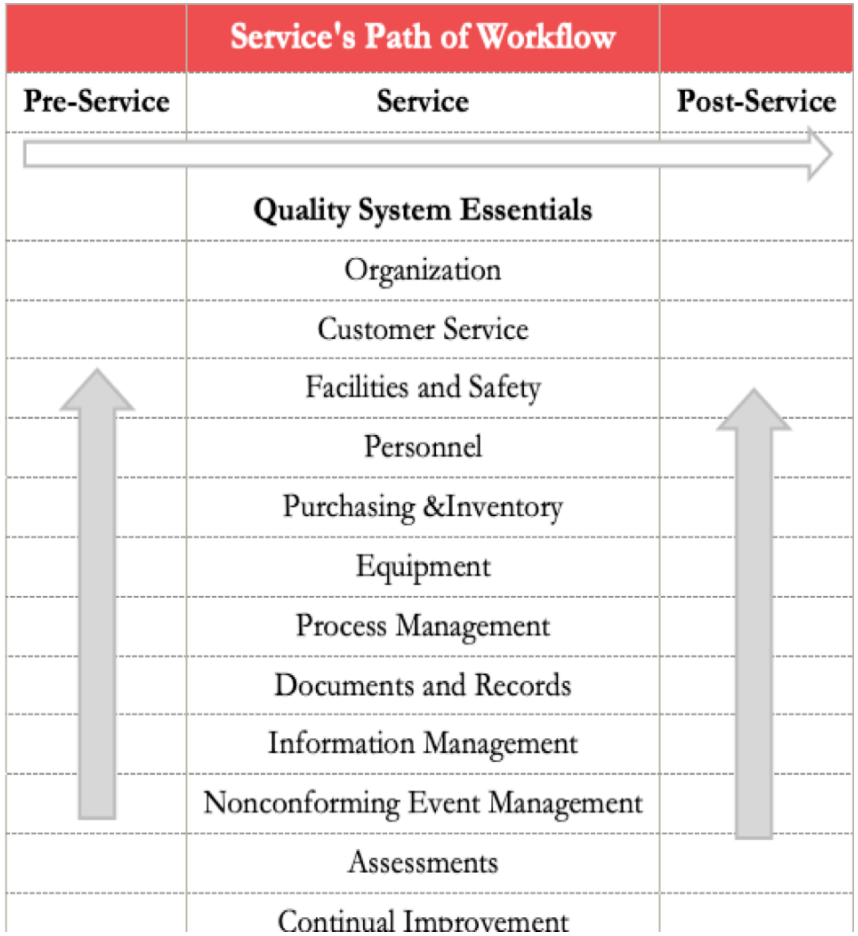


Figure 2. QSE Path of Workflow

Review the list of management principles in figure 2 and compare to the existing processes in your laboratory. Document the QSE that has not previously been addressed in some form.

These principles can be in the form of policy, process, procedure and/or existing practices. Document on Module 2 Form 5 of the workbook.

For a comprehensive description of each QSE: **Quality System Essentials Lecture MD General 2014 Course, Clin Path Ain Shams University, Egypt**. 12 Quality System Essential Description

Phase III Pre-Assessment

	PRE-ASSESSMENT AND DOCUMENT CONTROL ACTION ITEMS: Confirm the following:				
	Document all activities **not previously** implemented:				
		Choose all that apply			
	QSE Clause Example	**Policy**	**Procedure**	**Process**	**Training**
1	Occurance Management				
2	Assessments				
3					
4					

Module 2 Form 5

Instructions:

1. Review the 12 QSE clauses
2. From the 12 QSE's, document the clauses **not previously implemented** in the laboratory on module 2 form 5.
3. Provide an X for all that apply

Action Item

Take note of all QSE not previously implemented within the laboratory

01 Activities for Compliance

	Quality System Essentials (QSE)	Activities for Compliance	
Quality System Requirements (CFR)	Management responsibility	Quality policy	Quality planning
		Organization	Quality system procedures
		Management review	
	Quality audits		
	Personnel		
Subpart C, Design Controls	Design controls	Classification rules	Design verification
		Design and development planning	Design validation
		Design input	Design transfer
		Design output	Design changes
		Design review	Design history
Subpart D, Document Controls	Document controls	Document approval and distribution	
		Document changes	
Subpart E, Purchasing Controls	Purchasing controls	Evaluation of suppliers, contractors, and	
		consultants	

Activities for Compliance
The activities for compliance list include tasks pertaining to each clause. This document is intended to assist the leaner understand the clauses in more detail.

The results of the pre-assessment will provide insight into the work needed to build a comprehensive regulatory quality framework.

The findings from the assessment will serve as a checklist of needed policies, procedures and processes.

Module 2 Form 7

Crosswalk II: QSR in Comparison to Your Laboratory

21 CFR 820 Quality System Regulation
Management Responsibility
Quality Audit
Personnel
Design Controls
Document Controls
Purchasing Controls
Identification and Traceability
Production and Process Controls
Acceptance Activities
Nonconforming Product
Corrective and Preventive Actions
Labeling and Packaging controls
Handling, Storage, Distribution and Installation
Records
Servicing

Module 2 Form 6

Review the clauses in the 21 CFR 820 and compare the clauses to existing processes in your laboratory.

Document the clauses that has not previously been addressed in some form.

These clauses can be in the form of policy, process, procedure and/or existing practices.

For more information:

21 CFR 820

Phase III Pre-Assessment

	PRE-ASSESSMENT AND DOCUMENT CONTROL ACTION ITEMS: Confirm the following:				
	Document all QSR Activities **NOT implemented** that would otherwise adhere to standard:				
		Choose all that apply			
	QSR Clause	**Policy**	**Procedure**	**Process**	**Training**
1	Purchasing				
2					
3					
4					

Module 2. Form 8.

Instructions:

From the **QSR** clause detail worksheet, document the clauses **not previously implemented** in the laboratory. Choose all that apply.

Document on Module 2 Form 8 of the workbook.

For a comprehensive description of each QSR: 21 CFR 820

Action Item

Take note of each unaddressed QSR clause. Develop a list of guidance documents. Develop a guidance document to address the clause or expand the topic within existing guidance documents to include each requirement.

Crosswalk III: QSE in Comparison to QSR

QSE		QSR
12 Quality System Essentials		21 CFR 820 Quality System Regulation
Organization		Management Responsibility
Personnel		Quality Audit
Equipment		Personnel
Purchasing and Inventory		Design Controls
Process Control		Document Controls
Document and Records		Purchasing Controls
Information Management		Identification and Traceability
Occurrence Management		Production and Process Controls
Assessments		Acceptance Activities
Process Improvement		Nonconforming Product
Facilities and Safety		Corrective and Preventive Actions
Service and Satisfaction		Labeling and Packaging controls
		Handling, Storage, Distribution and Installation
		Records
		Servicing

Module 2. Form 6.

Next Step: Compare the QSE to adherence of the clauses listed within 21 CFR 820.

Take note: Activities included in QSE may differ and may not equate equally to a similar clause within the 21 CFR 820.

For details see the 21 CFR 820 standard at 21 CFR 820 Standard

Phase IV Design Control

21 CFR 820

21 CFR Design Control	Description
Design and Development Planning	Guidance regarding the plan, design, development, execution, involvement, interface with different groups and responsibility
Design Input	Procedure that describes regarding the intended use of the test, user needs and the process to manage and resolve discrepancies. The process includes, responsibility approval, documentation and rationale at every step
Design Output	Procedure that describes the output of the design provides rationale, performance, specification and verification that the design successfully transferred into the testing environment
Design Review	Procedure: describes the process to review all phases of the design with, documentation and approval all at each step. Establish and maintain procedures for the identification, documentation, and validation, verification, review, and approval of design changes before implementation
Design Verification	Procedure: The test is safe, effective for use, conforms to the needs of the user and meets its intended use to ensure the design works as intended and has been verified, documented and approved at each activity
Design Transfer	Procedure: describe the accurate transfer of design into manufacturing requirements
Design Changes	Procedure: The process to identify, track, document and approval changes prior to each activity
Design History	A means to track processing information pertaining to design, development, testing and links with all other design controls to demonstrate traceability and approval for each LDT manufactured
Medical Device Reporting (MDR)	Procedure: Describing a process to identify, document and report an adverse event because of the test

Module 3. Form 9

Design control is similar to a product development methodology that begins at test development and ends at the conclusion of the test.

The application of design control includes all aspects of test development, review, verification and manufacture.

Design control activities may or may not exist or in some form in the laboratory.

Phase IV Design Control

DESIGN CONTROL ACTION ITEMS: Directions
For each element of design control as depicted in Figure. 21, develop pertinent guidance documents describing LDT activities specific to the processes performed in the lab.
Example:

Document all QSR Activities **NOT implemented** that would otherwise adhere to standard:

	Choose all that apply			
Design Control	**Policy**	**Procedure**	**Process**	**Training**
Design planning and development				
Design input				
Design output				
Design review				
Design verification				
Design validation				
Design transfer				
Design changes				
Design history				
Design transfer				

Module 3. Form 10

Instructions:

1. Review each clause of design control.
2. On the assessment worksheet Module 3 Form 10 identify each clause of design control that exists in some form in your laboratory. Choose all that apply.

Action Item

Take note of any policy or procedure associated with Design Control activities that may exist in the laboratory.

From the results of the crosswalk: We now have the list to develop necessary guidance documents for a QMS framework.

Building a LDT Structure

An LDT structure includes a process for test development not advancing until the go/no go determination is made at each step. The steps are called stage gate and each gate is assigned a process owner that will manage a list of tasks and activities to be completed. As shown in Figure 3, a manager is assigned at discovery and the project then moves through design, development, testing, validation and launch.

The process is further managed through the assignment of a cross-functional team at each gate for a go or no-go decision at handoff. The teams are responsible to document details, to obtain approvals and to initiate a list of missing activities associated with each gate.

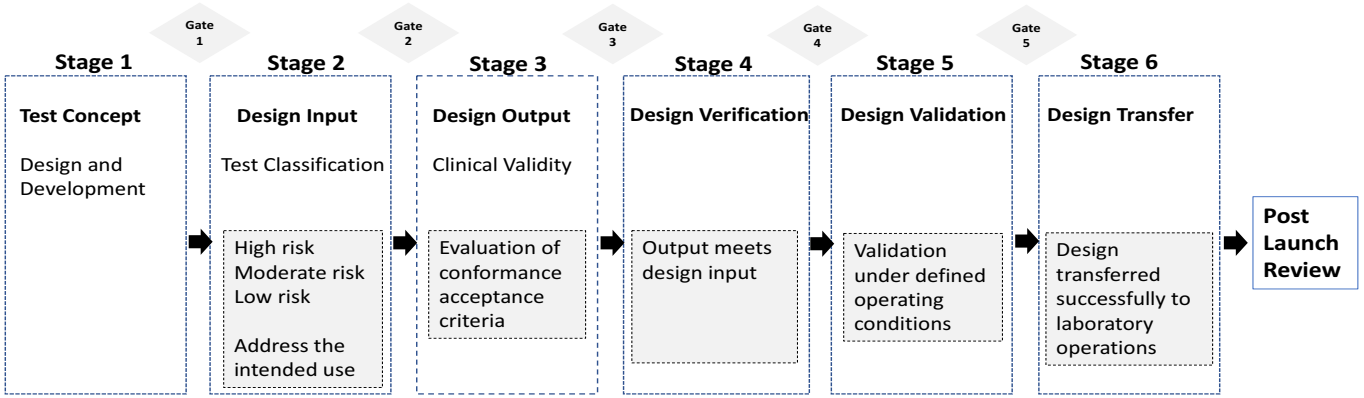
By clearly communicating requirements, this approach to an LDT launch will expedite the process and will allow for just-in-time response and resolution to meet rapidly changing needs. A comprehensive review is managed, performed and documented at each step. The documentation is captured as described by design control through the process of design history file.

A post LDT launch meeting is conducted to discuss lessons learned and to identify potential changes for the next launch.

Phase V. Stage Gate

Adoption of an Agile Stage Gate Hybrid Technique for LDT development

Product development methodologies applicable to LDT divide Design Control activities into stages separated by decision points. The steps of Design Control are listed as a go (approval)/no-go (rejection) decision point at each stage. All changes are captured and documented at each step.



Stage Gate step includes the following:

1. Inspection at each step
2. Design change
3. Design history
4. Design review

Phase V. Stage Gate

An owner is assigned to oversee the process, manage the team, follow-up on progress and ensure stage gate responsibilities are conducted.

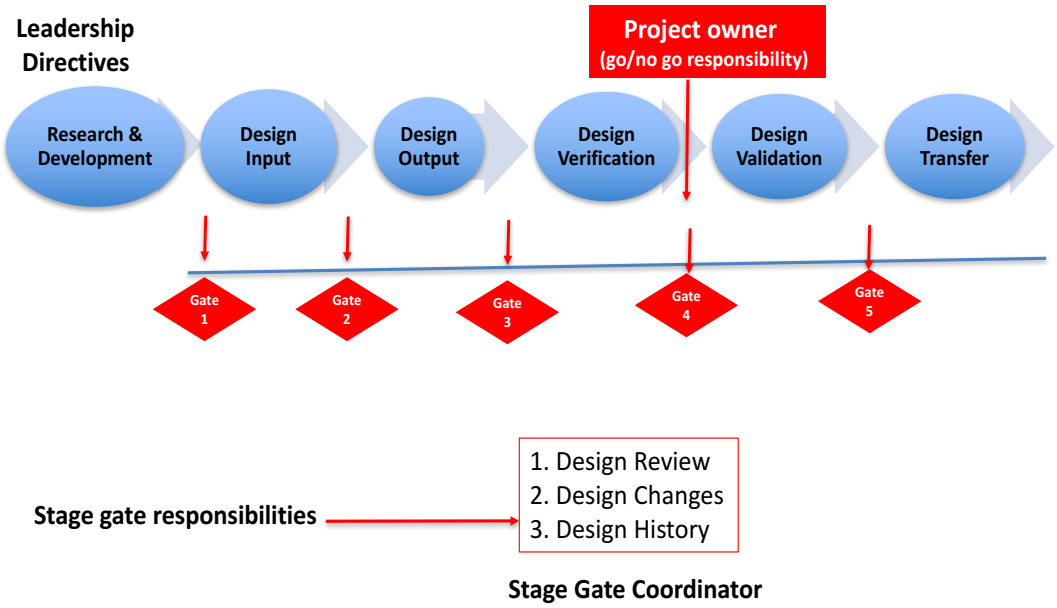


Figure 4. Stage Gate owner responsibility

Action Item

Develop a stage gate process to include design control with a go/no go owner, cross functional team and a process to document all changes.

Phase VI Validation

The (PQ), (OQ) and (PFQ) Sections of the Validation Protocol

Process Qualification (PQ)	
Item	Importance
Research Design approval	
Employees are trained	
Equipment maintenance	
Polices developed/revised	
Supplies planned in advance	
Equipment validation	
Design control guidance	
Origin of an LDT	
Proof of Concept	
Protocol: Design & Development	
Input & output design	
*Quality control documentation	
* Equipment validation	
* Training records	
* Testing equipment	
* Materials / reagents	
* Supplier Qualification	
Regulatory guidelines	

Operational Qualification (OQ)	
Item	Importance
Test protocol is complete	
Patient/Clinician involvement	
Guidance documents	
Supplier qualification/performance	
Quality control	
Standardized processes	
Design transfer	
Design changes	
Design history file	
Design validation	
Equipment validation	
Gaps - regulatory requirements	
Gaps in the process	
Supervisor oversight	
Electronic tracking	

Performance Qualification (PFQ)	
Item	Importance
Quality control checks	
Reagent QC testing	
Available supplies/reagents	
Process owner management	
Discrepancies are noted/resolved	
Document control	
Employees are trained & competent	

Figure 5. Validation activities

A validation protocol ensures the entire process is working as intended. The sections of the protocol include the following:

Process Qualification: (PQ) ensures the necessary components of the process are implemented according to design specifications. Documents necessary for operation, performance and maintenance are identified and the process includes all pertinent factors.

Operational Qualification: (OQ) will ensure verification, documentation and the process is operating as intended.

Performance Qualification: (PFQ) demonstrates the process consistently produces the same result and operates correctly when used at defined capacities. Test the entire system within the designed processes and document the response. Perform any quality checks on tests.

Phase VI | Validation

Validation Summary and Approval

Validation will test the overall process to ensure the system is performing as intended

Note: Any validation requirements that have not passed require investigation before use.

Instructions:

The following criteria will support the conclusion. Check all that apply:

- The process is in compliance.
- All steps have been executed to completion.
- All discrepancies have been recorded and successfully resolved.
- The process is not in compliance. *(Describe in Comments)*

In the event the validation plan fails, the following approval/rejection criteria is denoted as follows:

- Failed, but retested and processes are in place to prevent the reoccurrence

Action Item

Develop (PQ), (OQ) and (PFQ) sections of the validation protocol that will be used to ensure the process as operating as intended

Phase VII | Development of a QMS

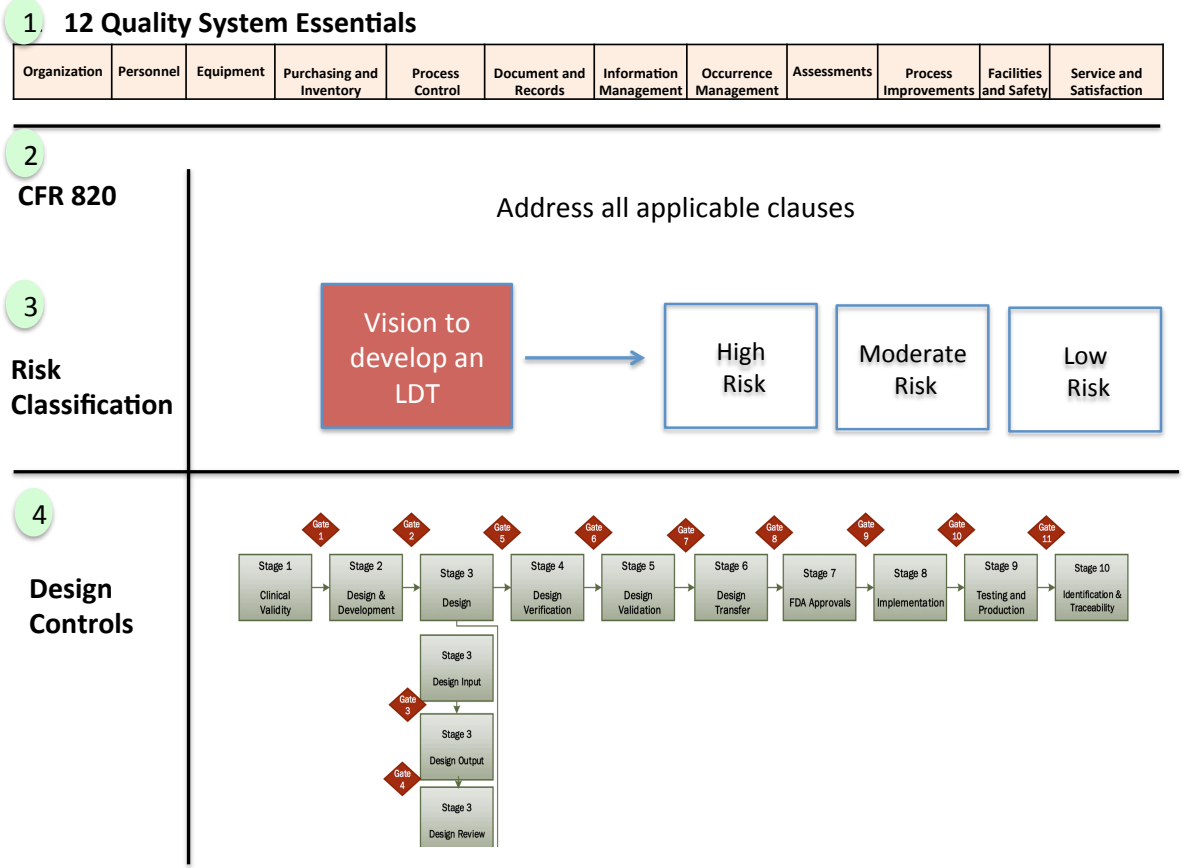


Figure 6. Development of a QMS

The development of a comprehensive quality management system include:

Step 1: The QMS begins with the adoption of the 12 QSE

Step 2: addresses the establishment of guidance documents for clauses within the 21 CFR 820 regulatory requirements not already included in the 12 QSE

Step 3: describes the process for classifying LDT risk--high, moderate or low risk. Regardless of the risk classification, the support structure of the quality management system remains stable

Step 4: Development of polices processes, and procedures specific to each element of design control

Action Item

Develop a guidance document to address each unaddressed QSE and QSR clause along the Path of Workflow.

Phase VII Development of a QMS

- The framework consists of policies, procedures, structure, resources, appropriate regulations, operational requirements, and organizational methodology
- Integration of the 12 QSE, elements in the 21 CFR 820 previously and design control
- **Follow the seven phases of QMS development as follows:**

Action Item

Instructions:

1. Understand requirements
2. Cross reference the existing 12 quality system essentials to match the common 21 CFR 820 clauses
3. Perform an assessment to determine current laboratory policies, procedures and process
4. Based on the results of the gap analysis and procedure assessment, develop missing guidance documents to include design control
5. Implement tasks associated with stage gate, agile methodology and assign a responsible person(s) to perform go/no go decisions at each handoff.
6. Develop a quality management system framework to include the above

Acronyms

1. CLIA- Clinical Laboratory Improvement Act
2. CFR- Code of Federal Regulations
3. FDA- Food and Drug Administration
4. CLSI-Clinical Laboratory Standards Institute
5. QSE- 12 Quality System Essentials

Figures

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