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An Agile Quality Management System For Laboratory Developed Tests

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AN AGILE QUALITY MANAGEMENT SYSTEM FOR LABORATORY DEVELOPED TESTS

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS AND TERMS

Acronyms

CFR	Code of Federal Regulation
CLIA	Clinical Laboratory Improvement Act
FDA	Food and Drug Administration
ISO	International Organization for Standardization
QMS	Quality Management System
QSR	Quality System Regulation
QSE	Quality System Essentials

Definition of Terms

1. **Adverse Event -** An adverse event is any undesirable experience associated with the use of a medical product that could result in harm or death to a patient. [2]
2. **Laboratory Developed Tests** - The FDA defines the term (LDT) as an IVD that is intended for clinical use and is designed, manufactured and used within a single laboratory. [2]
3. **Enforcement discretion-** Rather than a mandate it is the authority for the agency to take action if safety concerns are identified. [2]
4. **CLSI** - (CLSI) **Clinical Laboratory Standards Institute:** a not-for-profit membership organization that brings together the global laboratory community for a common cause by facilitating a unique process of developing clinical laboratory testing standards based on input from and consensus among industry, government, and health care professionals. [24]
5. **ISO 9001** - a quality management system (QMS) standard that requires an organization to meet its own requirements and those of its customers and regulators. It is based on the plan-do-check-act methodology, which helps organizations establish, implement, monitor and

measure their processes to deliver results that align with the organization's requirements and continually improve performance by taking appropriate action. [38]

6. **College of American Pathologist (CAP)** - a laboratory accreditation agency that empowers CAP members and customers to achieve excellence in the practice of pathology and laboratory medicine. [13]
7. **Quality Management System** - formalized business practices that define management responsibilities for organizational structure, processes, procedures and resources needed to fulfill product/service requirements, customer satisfaction, and continual improvement. [37]
8. **In-vitro diagnostic (IVD) tests** - are those reagents, instruments, and systems intended for use in diagnosis of disease or other conditions, including a determination of the state of health, in order to cure, mitigate, treat, or prevent disease or its sequelae. Such products are intended for use in the collection, preparation, and examination of specimens taken from the human body. [21 CFR 809.3] [14]
9. **Clinical validity** describes the test's ability to predict a given clinical outcome [3]
10. **Premarket Approval** - any premarket approval application for a class III medical device, including all information submitted with or incorporated by reference. "PMA" includes a new drug application for a device under section 520(l) of the FD&C Act. [41]
11. **Quality System Regulation** - organizational structure, responsibilities, procedures, processes, and resources for implementing quality management. [41]
12. **Total Quality Management**- a management approach to long–term success through customer satisfaction. In a TQM effort, all members of an organization participate in improving processes, products, services, and the culture in which they work. [43]

CHAPTER 1: INTRODUCTION

'It must be remembered that there is nothing more difficult to plan, more doubtful of success, nor more dangerous to manage than the creation of a new system. For the initiator has the enmity of all who would profit by the preservation of the old institutions and merely lukewarm defenders of those who would gain by the new ones.'

Niccolo Machiavelli (1469 - 1527)

Healthcare within the past several decades have seen an impetus towards precision medicine leading to "dramatic changes in how health care is delivered." [1] This growth has generated an expansive industry that produces genome- and molecular-based laboratory tests, reagents and protocols required to detect and treat illnesses. In the laboratory, these new diagnostic methods are referred to as "Laboratory Developed Tests" or LDT. [2] LDT are defined as a sub-set of in vitro diagnostics (IVDs) that are "intended for clinical use and designed, manufactured and used within a single laboratory".[2] Historically, tests were developed by medical laboratories on a small scale, but as the interest in molecular testing expanded, large diagnostic manufacturers also began to develop and mass market LDT.[2] (3) Governmental public safety agencies became interested in the marketing claims stated by these manufactures and the accompanying medical outcomes.[4]

In 2004, poorly validated research alerted the FDA to a laboratory industry that lacks regulatory oversight and structure for design, development and testing of LDT. [56] Historically, laboratories were under enforcement discretion by the Food and Drug administration and have adverted the approval process as required for laboratory test kit manufactures under the medical device act F, D & C and 21 CFR 820.[4] The test registration and regulatory approval process is difficult to manage and according to the Centers for Medicare & Medicaid Services (CMS), there

are approximately 254,000 laboratory entities in the U.S. with 335,700 medical technologists and technicians. In addition, the expansion of genetic testing also contributes to the complexity and introduces a significant amount of test variation to field of LDT. [11, 61]

In addition, a significant gap exists between the Clinical Laboratory Improvement Act (CLIA) established for laboratory accreditation and FDA regulations.

To address this issue, the FDA proposed a rigorous approval process to reduce or eliminate the potential for error in healthcare like that required for manufacturers of medical device in a draft guidance entitled *Framework for Regulatory Oversight of Laboratory Developed Tests.*[3] In this draft guidance, the FDA presents the agency approach for LDT oversight as a public health risk". [2, 3] In addition, the FDA proposes a process for risk classification, time frames for LDT registration, a formalized design control structure and a phased implementation plan for a Quality System Regulation (QSR) for laboratories that register LDT for high risk or moderate risk classifications.[2] Laboratories developing rare LDTs are exempt from the requirements described in the proposal because as described, the outcome of an incorrect result or incorrect interpretation is unlikely to affect morbidity, mortality or the safety of patients. [3]

This QSR management structure is presented from a medical device perspective and encompasses a structure consisting of management responsibilities, procedures, processes, and resources to ensure patient safety. Laboratories disputed the FDA oversight and QSR structure comprised of medical device requirements and challenged the applicability to diagnostic testing. [42] Many laboratories may lack the resources or regulatory understanding to develop a quality system program that meets FDA specifications.[44]

The draft guidance resulted in significant resistance from the laboratory community and following a period of public comment, the Agency announced, in a Discussion Paper dated January

13, 2017, that they were considering possible alternatives to the original framework. [6,7] The FDA continues the proposition for regulatory requirements from the 2014 draft guidance and emphasizes the adoption of a (QSR) for the development of LDT that include design controls, acceptance criteria and corrective and preventive action procedures as referred to in the 2017 Discussion Paper. [6,] Moreover, the laboratories continue to struggle to understand the implications of this additional regulatory oversight, and their responsibility to comply in the event the draft guidance becomes policy.

Motivation for this Research

The motivation of this study is to understand regulatory requirements, laboratory constraints and necessary factors to design, develop and implement a regulatory quality management system for laboratories that perform high risk and moderate risk LDT. In the absence of a required laboratory accreditation quality management system standard, I will explore requirements as mandated for the medical device industry and understand how these principles especially product development methodology of design control may align and be applicable to laboratory testing. [14]

Through this study I will investigate, develop, design and address management practices that will best support unique product variation, accuracy of results particularly important for addressing the patient safety concerns of the FDA and speed of processing within a high -volume routine automated laboratory. The framework will incorporate process standardization to support manufacturing requirements of product, people and service. I will explore the applicability of the agile product development technique to a laboratory environment that will assist laboratories comply with all pertinent regulations and expedite test development. [47]

The problem is as follows: If the FDA mandates an adoption of a Quality System Regulation for the process of Laboratory Developed Tests, how will laboratories design, adopt and implement a quality management system that commit to this requirement.

Research Goals

The inspiration to conduct this research is expressed through my lifelong commitment and contribution to positively affect healthcare. My career began in a recovery facility where I cared for the sick, elderly and disabled and it was there that I developed a concern for the welfare of people who were unable to care for themselves. It was through this experience that I discovered my passion for patient safety and consequently has persisted as the focal point of my work. I spent many years in laboratories and later as a consultant that assisted leadership achieve increase levels of quality through waste elimination and process standardization. This research study to explore the perceived apprehension associated with laboratory testing, the associated literature review and the call for action by governmental agencies opened my eyes to a reality of an industry that lacks regulatory controls and oversight for diagnostic tests, a service, that clinicians and patients depend for treatment decisions.

From a practical perspective, the proposed FDA recommendations, if implemented effectively, could transform healthcare on a global level and set the world standard for global laboratory quality.

The scholarly goals of the proposed changes as recommended by the FDA can be described as an impetus to change within a historically stable regulatory laboratory environment. These recommendations by the FDA may guide the current state of laboratories into futuristic change.

Scope of this Research

The scope of this research is limited to laboratories actively developing in house high risk and moderate risk LDTs within a system that has yet to understand, define and implement regulatory processes that align with pertinent regulations for patient safety as proposed by the FDA. The development of rare LDTs is out of the scope of this research due to the exemption status described in the 2014 draft guidance for LDT. The outcome of an incorrect result for a rare LDT is unlikely to affect morbidity, mortality or the safety of patients. [3]

Research Questions

The following research questions have been proposed:

1. Can laboratories operationalize a quality management framework that will meet FDA requirements?
2. Will an adoption of a quality system framework provide the manufacturing foundation that will adhere to 21 CFR 820 Design Controls?

CHAPTER 2. LITERATURE REVIEW

This literature review will outline the history of LDT, regulatory involvement and the current condition within the scientific community regarding laboratory-developed tests.

The Laboratory Improvement Amendment Act (CLIA) 1988 was developed and enforced under the direction of the Centers of Medicare and Medicaid Services (CMS) and was passed to assure the safety of the American healthcare system in general and specifically to oversee laboratory testing. The objective of this legislation is to ensure the integrity of laboratory testing and results. ‘‘12

Although CMS has oversight for laboratory accreditation, the Governmental Accounting Office (GAO), conducted a study for commercially manufactured home genetic testing kits marketed and sold to consumers that were noted to provide little medically useful information and worst, test results “were misleading and of little or no practical use”. [4] To circumvent these issues, two bills were introduced to allow the FDA to hold LDT manufactures to the same standard as medical device firms. The bills were not passed and although their actions have become a source of controversy, the FDA preemptively assumed oversight over the manufacture and regulation of all LDT.[4]

Since the bills were introduced to congress, the FDA has identified problems with several high-risk LDT that includes: “claims that are not adequately supported with evidence; lack of appropriate controls yielding erroneous results; and falsification of data”. [5] The FDA is concerned for patient safety and the potential outcomes of unregulated tests for a “health condition that could result in illness or death.” [5]

Although, the FDA was given oversight and authority over diagnostic testing [17] and regulate manufacturers and devices under the Federal Food, Drug, and Cosmetic Act (FFDCA), CLIA

retains oversight to ensure clinical laboratories operate as described in federal regulation 21 CFR 493.

Healthcare systems aboard are vastly different. As early as 1990, the United Kingdom instituted regulations that consisted of the establishment of clinical governance to regulate quality systems in healthcare and to hold each organization liable for outcomes. As a result, the goal to eliminate poor quality for the best interest of the patient is demonstrated through continuous improvement, risk management and the establishment of processes to minimize errors. In the NHS, all leaders are responsible for quality outcomes by managing adverse events, customer complaints, and by ensuring that policies and procedures are implemented for all elements of the system [62]

Concerns from Professional Societies

Unlike the NHS, many organizations have objected to the FDA's oversight of LDT, including the American Hospital Association, the American Cancer Institute (ACI), and the American Clinical Laboratory Association (CLA). The American Medical Association has stated "the FDA proposal will add an additional layer of regulatory requirements which may result in patients losing access to timely lifesaving diagnostic services and hinder advancements in the practice of medicine." [21]

The CLA has argued, "The FDA requirements would stifle laboratory innovation and retard patient access to critical diagnostics." [3] Moreover, the academic laboratories if held to the 21 CFR 820 standards may be required to perform clinical trials for each new genetic test developed. This process would require additional resources and as explained by Evans, (2015) "laboratories have insufficient resources to meet the proposed requirements and would essentially be precluded from developing or even improving tests in response to patient needs, clinician demands and changing technology." [10] The perceived outcome of an innovation may influence professional groups to

abandon processes advantageous to patient safety and Sanson-Fischer, (2004) explains "If a proposed change alters the balance of power between or within professional groups in a "negative" way, the innovation may not be implemented."[22] To eliminate complexity and shorten the approval time for new test development, the FDA is currently seeking the advice of a steering committee that consists of multiple organizations and professional agencies to agree on a path for the best interest of patient safety. [22] The FDA proposed framework lacks formal structure, tools standardization and defined rules for use.

Process Standardization

A standardized harmonious approach or mandate for quality and standardization has not been defined for US laboratories. Outside of the laboratory, many industries have adopted practices aligned with quality standardization, however, successful implementation is based on the support of leaders to own and drive an organic, directed initiatives with tasks and activities applied to local specific organizational processes. As W. Edwards Deming secretary stated in a 1989 video, "American managers would like to choose and implement quality from a Chinese menu, but there is no instant pudding. Quality doesn't work that way." [23]

Total Quality Management

The standardization of organic processes can be found described in a 20-year-old interpretation of a Deming management philosophy, known as Total Quality Management (TQM). Continuous improvement, employee empowerment and standardization were at the heart of the successful application of Deming management principles as applied to the Toyota Motor Corp. This success story was described by academic scholars at major US institutions such as: MIT (Womack,1990), Harvard (Spear and Bowen 1999) and University of Michigan (Liker, 2004). [30, 31, 33] Toyota's brand of TQM came to be labeled as 'Lean' referring to the bufferless production

system by a graduate student of Womack named John Krajcik (Krafcik 1988) former CEO of Hyundai America.

Outside of Toyota, one of the best examples of an TQM initiative in healthcare was of a new hospital CEO, Charles Evans of Memorial Hospital, Jacksonville, FL in 1991 (Case 1995) touting TQM as key to culture change. [30] However, no subsequent publications described or were issued by this institution. In fact, search of this hospital's current website 22 years later shows neither trace of that CEO nor any mention of a culture of continuous improvement, TQM, Lean or Deming. This is typical of the archeology of TQM and is described by a (quotation-George Santayana) "Those who cannot remember the past are condemned to repeat it."

Continuous improvement efforts with new names continuously emerge as the flavor of the year, however, have organizations altered their management approach to change?

As referenced by Gatchalian, 1997 the most common reasons for failure in creating successful cultures of continuous improvement, were associated with problems of sustainability of leadership and purpose, absence of strategic communications and teamwork for quality improvement, and lack of total commitment to the Deming management /TQM philosophy and practice. [34] These in turn were derived from poor understanding of the Deming philosophy by upper management and a general lack of employee opportunities to relate training activities with company mission/vision or directions. [35] Implementation of TQM follows an historic repetition of similar practices per Naslund, (2008). [36] Organizations continue to re–invent the wheel, but never pause to self-reflect on the lessons of the past. A description of this similar pattern has been described as the seven-stage life cycle of a fad for Total Quality Management and early phases of the life cycle cited by Naslund (2008) in relation to the current enthusiasm for Lean management in healthcare. [36]

The life cycle is described as follows: An academic article is written on a new discovery or theory;

1. The study is discussed, summarized, and repeated;
2. The concept is popularized in a best- selling book;
3. Management consultants carry new techniques to their client base;
4. Managers embrace the fad and champion the concept;
5. Time passes, enthusiasm dims, and doubts and cynicism arise; and
6. New discovers occur and consultant interest turns elsewhere.

TQM did not sustain and can be seen in the trend of publications, indicating original initiatives or the buzz, peaking in the early 1990s and then trailing off.

CHAPTER 3. FACING THE INEVITABLE: BEING PREPARED FOR REGULATORY REQUIREMENTS FOR LABORATORY DEVELOPED TESTS

Overview

This chapter address an application of a standard manufacturing approach to the laboratory is described through the application of a research design for development of a Quality Management System titled *Facing the Inevitable: Being Prepared for Regulatory Requirements for Laboratory Developed Tests.* The objective was a call for action to educate the laboratory community by introducing terms, definitions and regulatory requirements. We discuss how these requirements may be applicable from the medical device industry to laboratory medicine. We performed nine interviews with laboratory professionals and as a result of the feedback developed and tested strategic factors by use of a survey that would comprise a quality management system framework with product development methodology to incorporate design control. This manuscript was sent for publication in the American Journal of Clinical Pathologists.

Introduction

Contemporary technological advances in laboratory medicine have led to a category of laboratory diagnostics known as Laboratory Developed Tests (LDTs). LDTs are defined as a subset of in vitro diagnostics (IVDs) that are "intended for clinical use and designed, manufactured and used within a single laboratory".[2] In recent years, the Food and Drug Administration (FDA) identified problems with several high-risk LDT and has cited concerns that "patients could initiate unnecessary treatment, delay or forego treatment altogether".[2] In addition to the FDA, other governmental agencies, and private organizations have challenged the validity, accuracy, oversight, and safety of in LDTs. The FDA has now proposed requiring "all in-vitro diagnostic (IVD) tests intended for use in drug or biologic therapeutic decision-making be held to the same scientific and regulatory standard" as medical device firms.[2]

Since medical device development is held to a stringent and lengthy regulatory approval process, there is significant apprehension regarding the potential for undue delays in test development and patient access should LDT be held to the same standard. Unlike the medical device industry, which is subject to the requirements of the FDA, clinical laboratories are under the jurisdiction of the Centers for Medicare and Medicaid (CMS).[11] The FDA has proposed that laboratories adopt a formal risk-based classification and approval process, Quality System Regulation (QSR), and a formalized design control structure, as described in their 2014 draft guidance entitled *Framework for Regulatory Oversight of Laboratory Developed Tests.*[2] In this draft, the FDA proposes directives that are currently not mandated by CLIA or any other regulatory agency regarding laboratory oversight. Following a period of public comment, the Agency announced, in a Discussion Paper dated January 13, 2017, that they were considering possible alternatives to the original framework proposal. [6] Laboratories continue to struggle to understand the implications of this additional regulatory oversight and their responsibility to comply in the event the draft guidance becomes policy. Additionally, for those laboratories licensed by the New York State Department of Health (NYSDOH), the Wadsworth Center's Clinical Laboratory Evaluations Program (CLEP) has recently adopted a three-tiered, risk-based review and approval policy for all LDT submissions, effective November 14, 2016. Risk stratification is based upon an algorithm guided by three criteria: 1) well-established methodology, 2) key determinant of care assessment, and 3) the potential for patient impact.[7] It is interesting to note that in their recent Discussion Paper the FDA suggests the possible use of third-party collaborators, including the NYSDOH CLEP for review of LDTs. The Agency indicates that they are "exploring accepting NYSDOH review in lieu of its own".[6]

Motivation for the Research

The motivation for this research is to educate the laboratory community pertinent to LDTs by introducing terms, definitions, regulatory requirements and discuss the QSR as proposed by the FDA. We compare the requirements of the 21 CFR 820 to the recommended Clinical Laboratory Standards Institute (CLSI) 12 Quality System Essentials (QSE) for laboratories to understand how these principles may be incorporated and translated into laboratory processes that align and support the QSR. We also explore "design control" and discuss how these requirements for the medical device industry may be applicable to laboratory testing. We conducted interviews with laboratory professionals to gain an understanding of their concerns regarding the FDA draft guidance and translated that feedback into operational factors relevant for the development of a robust quality management system. Finally, we tested the factors for functionality, agility and usefulness through a survey and propose the design of a framework to assist laboratories prepare in the event the 2014 draft guidance becomes a policy.

Contribution: This paper contributes to the discussion about LDT by serving as a proactive call for action by educating laboratory professionals and providing the impetus to move from a wait-and-see approach to insight, knowledge and clarity that encompasses the many facets of LDT. We construct a means to collect substantiated data regarding the needs and gaps in laboratories and propose translation of those objectives into a vocabulary familiar to laboratorians. Finally, we translate and validate functionality and usefulness of strategic factors for design of a robust regulatory QMS by voice of customer.

Background

The literature provides a rich background regarding the history of laboratory developed tests. The FDA, other governmental agencies and private firms have challenged the validity,

accuracy, oversight and safety of laboratory testing. In 2008, Genentech, a private medical device manufacturer firm of oncologic pharmaceuticals and laboratory reagents, disputed laboratories or other companies selling LDTs or making statements without sufficient scientific evidence to support such claims.[8] Genentech petitioned the FDA to "require all in-vitro diagnostic (IVD) tests intended for use in drug or biologic therapeutic decision-making be held to the same "scientific or regulatory review".[8]

Since 2008, the FDA has identified problems with several high-risk LDTs; however, many organizations have objected to the FDA's oversight of LDTs, including the American Hospital Association, the American Cancer Institute (ACI), and the American Clinical Laboratory Association (CLA). The American Medical Association has stated "the FDA proposal will add an additional layer of regulatory requirements which may result in patients losing access to timely lifesaving diagnostic services and hinder advancements in the practice of medicine,"[9]

Certain professional organizations argue that the FDA lacks jurisdiction over LDT's, and the CLA has argued, "The FDA requirements would stifle laboratory innovation and retard patient access to critical diagnostics."[10] Moreover, the academic laboratories if held to the 21 CFR 820 standards may be required to perform clinical trials for each new genetic test developed. This process would require additional resources and as explained by Evans, (2015) "laboratories have insufficient resources to meet the proposed requirements and would essentially be precluded from developing or even improving tests in response to patient needs, clinician demands and changing technology."[10]

The FDA was given oversight and authority over in-vitro diagnostic medical devices in 1976; however, regulatory oversight for laboratories remains with CLIA.[1, 17]

Regulatory Overview

Clinical Laboratory Improvement Amendment (CLIA)

In this section, we highlight some of the important regulations that have led to the current framework governing LDTs. First, we discuss CLIA, next the medical device amendment, the FDA quality system regulations and compare how those regulations differ from laboratory accreditation.

The clinical laboratory has undergone progressive regulation over the past several decades, with key milestones depicted in Figure 1. The current regulatory framework has evolved from the Clinical Laboratory Improvement Amendments (CLIA) of 1967 and 1988, and is enforced under the direction of the Centers of Medicare and Medicaid Services (CMS). The initial intent of the CLIA 1967 amendment was to establish licensing requirements for laboratories across state lines; however, the legislation for CLIA 88 was established to update requirements, implement performance measures and add personnel responsibilities. Since 1988 the amendment has progressed to ensure validity, reliability, accuracy, and appropriateness of clinical laboratory testing and results.[11]

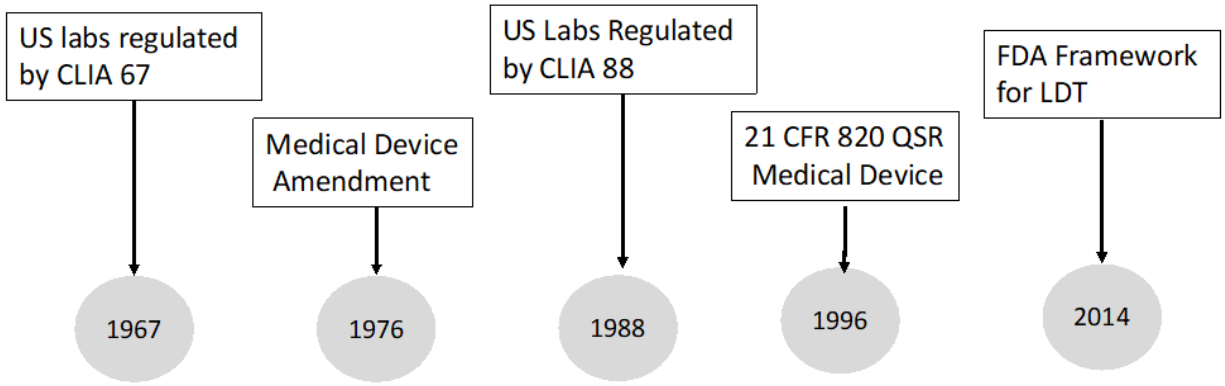


Figure 1: Timeline of regulatory oversight

Although the aim of CLIA is to ensure that clinical laboratories operate suitably,[12] Burd explains that CLIA lists the performance specifications as described in CFR 493 to be established, however, "does not specify the scientific methodology or implementation tool to be used."[12] CLIA instead defers selection of the appropriate methodology meeting these performance specifications to the Laboratory Director's judgement. Useful resources include not-for-profit agencies, like the CLSI, the College of American Pathologists (CAP), and the International Organization for Standardization (ISO), who develop and recommend clinical laboratory standards and accreditation criteria.[12] To this end, the CLSI has recommended implementation of 12 Quality System Essentials (QSE) (Table 1) as a "framework to a systems approach to managing quality".[24] The adoption of all 12 QSE will better ensure safe testing practices that align with governmental regulations.

Table 1: CLSI Quality System Essentials [24]

1. Organization	7. Process Management
2. Customer Focus	8. Documents and Records
3. Facilities and Safety	9. Information Management
4. Personnel	10. Nonconforming Event Management
5. Purchasing &Inventory	11. Assessments
6. Equipment	12. Continual Improvement

Medical Device Amendment

The medical device amendment was established in 1976 after 4.5 million Dalkon Shield intra-uterine devices sold between 1971-1974 adversely affected 900,000 women in the USA.[25] This device considered faulty was the impetus that promoted the establishment of FDA regulatory oversight to ensure the effectiveness of the intended use of medical device and to verify safe

manufacturing practices. The amendment required three classifications of medical devices: Class I- Low Risk medical devices; Class II- Moderate Risk; and, Class III- High Risk. The regulatory approval process differs significantly for each class of device. Class I devices require General Controls, Class II devices require pre-market notification (510(k)), and Class III devices require the most rigorous process of pre-market approval (PMA). These classifications of medical devices have not been a concern for diagnostic laboratories until the FDA's announced 2014 Draft Guidance for LDT. [26]

Quality System Regulation [21 CFR 820]

The 21 CFR 820 or Quality System Regulation (QSR) is a regulatory requirement that directs the methods for the design, manufacture, packaging, labeling, storage, installation and servicing of medical devices to ensure their safety and efficacy. [2] The QSR encompasses organizational structure, management responsibilities, procedures, processes, and resources for establishing and maintaining a quality management system and serves as a guide for organizations. The 2014 LDT draft guidance proposes the use of this existing QSR. However, LDTs differ from medical devices in three respects: 1) LDTs are considered by most outside of the FDA to be a medical service, not a device; 2) medical devices may be tested on human subjects and approvals may require additional time, processes, resources and regulatory requirements 3) Under the FDA, a device manufacture must demonstrate safety and efficacy of the product and may require verification through clinical trials for a (PMA) premarket approval for new devices or substantial equivalence for a (510K) predicate device. [1]

Differentiation Between Laboratory Developed Testing and Medical Device: Devices Cleared

The FDA cleared 2957 medical devices as 510(k) in 2012.[27] The average approval time for FDA internal review in 2012 was 168 days. As of September, of 2012 the FDA received 2965 devices, of which, 1715 were rejected with a refusal rate of 58%.[28]

In comparison, CLIA requires that tasks, activities and processes of diagnostic testing show accuracy and reliability of testing confirmed by validation of parameters and results. The FDA clinical trials are not equivalent to CLIA validation of testing parameters.

Similar to CLIA, the FDA does not provide the operational design template, detailed instruction or translation from medical device requirements essential for interpreting, extrapolating, designing and implementing a QSR

Table 2: Medical Device Requirements Regulation [26]

21 CFR 820 Quality System Regulation (QSR): Quality System Regulation requirements
ISO 13485: International Standard- Regulatory Quality Management System Requirements for Medical Device
Good Manufacturing Practices (GMP): Guidelines for manufacturing, testing, and quality assurance to ensure that a product is safe for human or animal consumption or use
Good Laboratory Practice (GLP): Principles to assure the quality and integrity of non-clinical laboratory studies

Comparing QSE to QSR

Parallel to the QSR, the 12 QSEs contain most of the broad management categories and elements found in the 21 CFR 820 (Table 3 is a side by side comparison of QSE to QSR, showing

where they are equivalent and how they differ.). [41] However, the extent of their applicability to laboratories differ. Without a step-by-step guide for establishing the operational structure required to comply with the QSR, laboratories may feel they lack the resources and funding to develop a quality management program that meets FDA specifications.

Table 3: Quality System Essentials in comparison to 21 CFR requirements

12 Quality System Essentials (QSE)		21 CFR 820 Quality System Regulation (QSR)
Organization		Management Responsibility
Customer Focus		
Facilities and Safety		
Personnel		Personnel
Purchasing and Inventory		Purchasing Controls
Equipment		
Process Management		Process Controls Production and Acceptance Activities Design Controls Identification and Traceability
Document and Records		Document Controls
Information Management		
Nonconforming Event Management		Nonconforming Product
Assessments		Quality Audit
Continual Improvement		

21 CFR 820: Understanding Design Control

"Design Control" was originally established as a guiding methodology for the design, development, manufacture and production of medical devices to ensure accuracy, reliability and quality are consistently built into every new device. The elements of 21 CFR 820 Design Control provide the manufacturing expectation of the FDA to produce a safe and effective product. [29] This methodology is an iterative process similar to product development methodology and although historically intended as a requirement for medical devices, the development of policies, procedures and processes as applied to test design should help with the establishment of design control specific to the laboratory. Figure 2. lists each element of design control from development to design history and Table 4 lists each element of design control with a modified description for the practical application to organizational processes. (Appendix C.)

Figure 2: Elements of Design Control for LDTs (21CFR 820)

Table 4: Description of Design Control [29]

21 CFR Design Control	Description
Design and Development Planning	**Procedure:** Set of processes that transforms requirements for an object into more detained requirements. Such as the plan, design, development, execution, involvement and interface with different groups and responsibility (ISO 9001)
Design Input	**Procedure**: Product characteristics, requirements, intended use, user needs and the process to manage and resolve discrepancies is defined.

	The process includes, responsibility approval, documentation and rational at every step
Design Output	**Procedure**: The output consists of technical, 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:** Describes the process that will ensure the test is safe, effective for use, conforms to the needs of the user and meets its intended use. The process to ensure the design works as intended, has been verified, documented and approved at each activity
Design Validation	**Procedure:** The process operates as intended under defined operating conditions
Design Transfer	**Procedure:** Describes the process of accurate transfer of the design into manufacturing requirements
Design Changes	**Procedure:** Describes 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:** Describes the process to identify, document and report an adverse event as an outcome of the test

*NOTE: Verification pertaining to Design Control and Validation host two separate meanings in the laboratory. [37]

Verification: Confirmation, through the provision of objective evidence, that specified requirements have been fulfilled. (design output meets the design input requirements)

Validation- Confirmation through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled. [37, 38]

Research Methodology

Now that we have covered the regulatory background, we turn to the technique conducted in this study as a mixed method approach to research employed in two sequential phases: Phase I consisted of qualitative interviews to capture the understanding of laboratory professionals in all aspects of LDTs and to determine if adherence to FDA regulatory requirements was achievable in a laboratory environment to design, develop, and test LDTs. If not, why not, and what would be the limiting steps.

In addition to the interviews, proceedings from the 2 Day FDA Work shop "Framework for Regulatory Oversight of Laboratory Developed Tests(LDT)" [39] held January 8-9, 2015 also contributed to this study. The intent of the workshop was for the FDA to provide the rationale for the 2014 draft guidance, invite feedback and participation from peers within the laboratory community to state their case for or against the 2014 framework in context of the proposed regulatory requirements. The interview and workshop information assisted the researchers identify factors that would serve as the building blocks for a regulatory laboratory framework.

During Phase II a quantitative survey was conducted to test the factors identified during the interviews to determine agility, functionality, and usefulness as a proxy in the absence of implementation in a live environment.

The study was designed as follows:

Phase I – **Interview:** A qualitative phone interview protocol was designed based on results of a review of the literature and was initially conducted to explore the potential challenges and constraints for laboratory compliance to the 2014 draft guidance. A convenience sampling strategy was used to select subject matter experts well versed in the historic, political and practical perspective of LDTs. The nine interview participants selected were professionals from the fields of laboratory, regulatory, accreditation, and medical device segments of the industry and who had the time or the availability to participate. (Appendix A.) The names of the interviewees and associated organizations are retained as confidential.

Secondary Data: The presentations obtained from the 2015 2 -Day FDA Work shop as it pertains to Quality System Regulation was documented, described and incorporated in this research. The public workshop was particularly helpful for this research and clarified issues and concerns as well as provided insight about future regulatory direction, strategy, and explained how FDA recommendations may affect future laboratory operations.

Constructing the Interview Protocol

The interviewees were asked the questions in the following protocol and were encouraged to discuss their knowledge of LDTs. The 30-minute confidential interview protocol consisted of nine questions (Table 5). (Appendix B.)

Table 5: Interview Questions

1. What is your role, title, and responsibility in the organization?

2. Tell me about the history and your knowledge about of Lab developed Tests?
3. What are some of the regulatory challenges associated with LDT's?
4. How does genetic testing influence regulatory oversight?
5. Describe the current scrutiny associated with regulatory guidelines for LDT's?
6. What is the role of the FDA in lab developed tests?
7. Explain the intent of the FDA guidance framework for LDT's released December 2014?
8. In your opinion, what would the implications(s) be if the FDA mandated regulatory guidelines for the process of LDT's?
9. How would you describe the "outcome and view of the future" if the FDA mandates regulatory oversight for LDT's?

Data Collection

The interviews were conducted by telephone over a two-year period from April 2015-May 2017. The process was explained prior to the interview, was audio-recorded when possible, and the results compiled. In addition to interview data, secondary data was collected from discussions that pertained to the quality system regulation during the public workshop to capture concerns with the 2014 draft guidance.

Data Analysis

The interviews were conducted with nine participants and the discussions were manually transcribed. The topics of the conversations were tallied for frequency and coded manually. As depicted in Table. 7 the interview and secondary data were categorized into codes and sub-codes, and a relational analysis was conducted to identify patterns of the most frequent theme and trends in both the interviews and the workshop discussion.

Phase II Survey: Testing the Functionality of the Framework

Constructing the Survey Protocol

A confidential Qualtrics Survey consisting of three sections was developed for this study. Section I includes survey statements derived from extensive literature searches, the qualitative interviews and a review of the 2015 2 - day FDA workshop pertinent to the QSR on Laboratory Developed Tests. Based on feedback, we translated the findings into a taxonomy comprised of eight strategic factors and 40 statements that serve as building blocks for a laboratory regulatory quality management system. As depicted in Appendix G, each statement contains five statements totaling 40 outcomes ranked on a 5 point Likert scale from "extremely important" to "not important at all".

The strategic factors identified are as follows:

1. Leadership commitment
2. Training
3. Pre-assessment of the current QMS
4. Design Control
5. Document Control
6. Process Control
7. Development of a QMS framework
8. Process validation

Section II contained two open-ended questions regarding the functionality, agility and usefulness of the strategic factors listed in the study. The feedback was instrumental in determining if the participants agreed with the factors included in the survey or in assessing their opinion about what factors would be more appropriate.

1) Do you agree with the strategic factors identified in the proposed framework for a Quality Management System of LDTs? If not, please suggest additional factors pertinent to develop a robust framework

2) Do you think the establishment of a Quality Management System framework will assist LDT laboratories incorporate regulatory requirements such as design control more readily? If not, why and what else is necessary?

Section III included two questions to substantiate the understanding of the respondents regarding LDT design, development, validation and delivery in a laboratory environment, and to document their professional role. The questions were as follows:

1. What is your professional role?
    a. Senior leader
    b. Medical Director
    c. Medical Doctor
    d. Technical Supervisor
    e. Manager/Supervisor
    f. Quality Professional
    g. Other
2. Do you consider yourself a subject matter expert on the topic of LDT?
    a. Definitely yes
    b. Probably yes
    c. Might or might not
    d. Probably not
    e. Definitely not

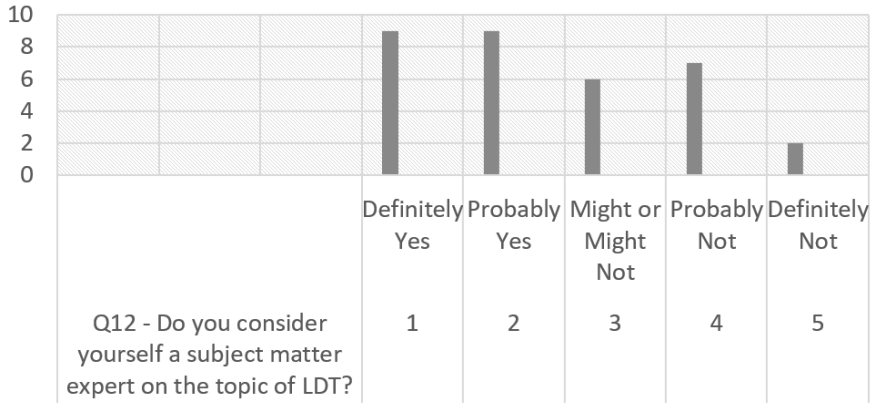
Data Collection

The quantitative survey was distributed to 767 laboratory professionals from April- July, 2017. The respondents included all attendees from the Executive War College Laboratory Conference held in May 2017 in New Orleans, LA. The survey was also distributed to randomly selected laboratory professionals demonstrating expert knowledge regarding the field of LDTs from LinkedIn with titles in the fields of regulatory, quality and medical laboratory.

Survey Demographics

The responses from the Qualtrics survey resulted in 51 started surveys and 35 completed surveys with a 69% completion rate of those who responded to the survey. The respondents included 10 senior leaders, four medical directors, 13 quality professionals, two technical supervisors, one manager and five other professionals. To ensure the appropriate expertise in the field of LDTs each participant was asked a critical qualifying question: Do you consider yourself a subject matter expert in the topic of LDT? Nine participants responded, "Definitely yes", nine "Probably yes", six "Might or Might not", seven "Probably not" and two "Definitely not" as depicted in Table 6.

Table 6: LDT Expert classification of survey respondents



Data Analysis

The statistical software SPSS Version 24 was used to calculate and analyze the scores for significance across all eight factors and 40 statements. The descriptive statistics include the mean, standard deviation and variance. Additional statistical analyses are as follows:

Principal Axis Factoring extraction method

The data was further analyzed by the Principal Axis Factoring extraction method, more specifically Principal Component Analysis with the Rotation Method: Varimax with Kaiser Normalization. According to Williams, (2010) isolating factors with high loadings can reduce the variables into a smaller set of factors, remove variation and cluster the relationships into patterns. This method was helpful to identify patterns consisting of high loadings with significant factors and statements exceeding 0.623 as depicted in Table 9. [40]

T-Test

The T-test was performed to determine whether the means of experts and non-experts had distinct, differing priorities and were *statistically* different regarding the adoption of a QMS. Since the participants rated four of five factors within the leadership commitment as the most relevant category, the assumption was the experts may have answered the statements differently due to their roles and responsibilities within the organization. The non-experts were operationally oriented rather than occupying a leadership role. To test this assumption, the data was analyzed to determine if experts and non-experts chose statements within the eight strategic factors differently.

Open –ended questions

The responses to the open-ended questions were analyzed using SPSS Version 24 to determine the number of participants considered an expert (Table. 6) and to tally acceptability and satisfaction with the suggested factors as explained in the survey results section.

Results

Interviews

The tone expressed by the interviewees was ambiguity and uncertainty regarding all aspects of the LDT process and similar concerns were articulated, including: 1) risk classification, 2) process validation to ensure the accuracy and precision of tests results, 3) the ambiguity of the 21 CFR 820 requirements translated to the laboratory 4) lack of clarity from the FDA and other governmental agencies (e.g., CMS) 5) the patient safety concerns of the FDA 6) lack of clarity and direction regarding the 2014 draft guidance.

The lack of coordination, clarity and guidance from CLIA and the FDA has created confusion and a lack of motivation on behalf of the laboratory community. The general feedback received through the interviews showed substantial ambiguity across laboratory professionals regarding terms, definition and how to transfer operational requirements into regulatory terms. In addition, it is unclear how the draft guidance would translate from medical device to the laboratory. The development of a laboratory application of 21 CFR 820 quality systems regulation that would meet the LDT manufacturing requirements has not been addressed by regulatory agencies and has left laboratory leaders unprepared to be proactive. Ambiguity also existed during the interviews regarding the definition of design control and how to appropriately address and translate these requirements into the laboratory environment.

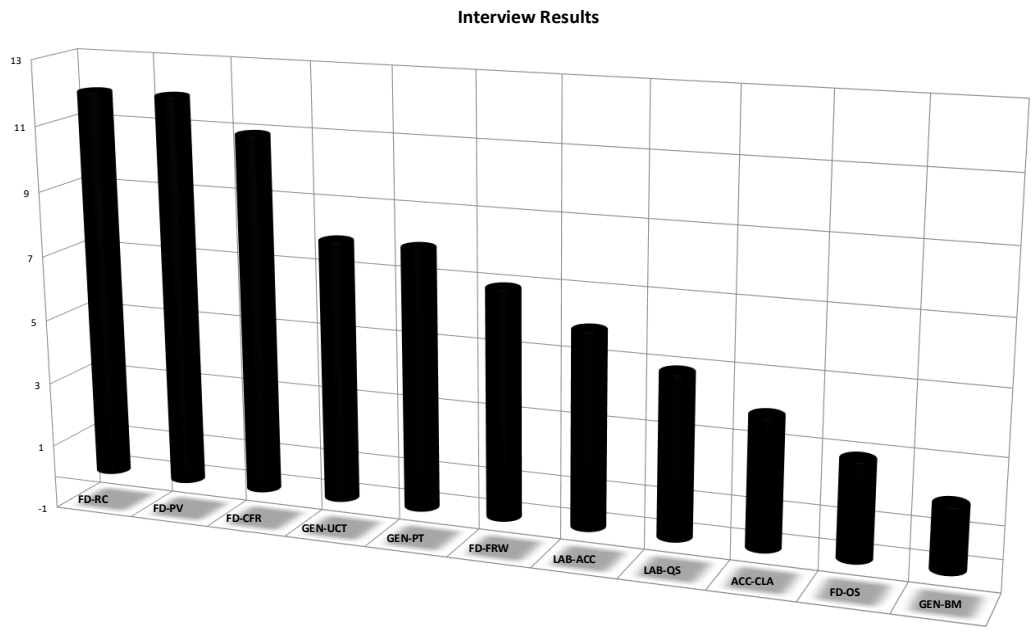


Figure 3: Interview Results

The discussion with the interviewees was instrumental to gain an understanding of the challenges faced by laboratory leaders, accreditation agencies and regulatory policy makers. The interview findings depicted in Figure. 3 illustrates the basis for the development of an operational framework for LDT. (Appendix F.)

The top 5 most significant concerns are identified as follows:

1. FD-RC: Risk Classifications

2. FD-PV: Process Validation

3. FD-21 CFR 820 QSR Requirements

4. GEN-UCT: Uncertainty

5. GEN-PT: Patient Safety

Table 7: Leading Interview Codes

Code	Category

General	
GEN- HT	History of LDTs
GEN- TN	Technology
GEN- PT	Patient safety concerns
GEN-DIR	The laboratory need for direction
GEN- BM	Change business model
GEN-UCT	Uncertainty of requirements and path forward
LAB	
LAB-Org	Hardship to organization
LAB-ACC	Accreditation requirements
LAB-QS	Quality Management Systems
FDA	
FD-RC	Risk classifications
FD-PV	Process validation
FD-FRW	FDA 2014 Framework proposal
FD-OS	Outsource may be necessary
FD-RS	Resources are needed to comply with regulations
FD-CFR	21 CFR 820 QSR requirements

Secondary Data

FDA Public Workshop

The information shared during a 2 day FDA webinar held January 8-9, 2015 made a significant contribution to this research. [39] The FDA began the conference by addressing areas of concern regarding the overview of LDTs draft guidance and the implication of adverse test results for the patients and the laboratories, and how the guidance would affect regulatory agencies already lacking appropriate resources. The director of the Centers for Devices and Radiological Health Jeffrey Shuren, stated that the "FDA is transparent and does not claim they got it all right and some say they didn't get anything right". However, the FDA is acting on the behalf of patient safety, which has made its way into the popular press. [39] In fact, Adverse patient safety concerns associated with LDT was published in literature: New York Times Aug. 28, 2008, July 7, 2011 and January 22, 2011. [39] Guest speakers shared their support and apprehension of the draft guidance and addressed the importance of test accuracy for appropriate therapies. Katherine Tynan, (2015) [39] a presenter stated "Quality systems vary significantly in terms of scale and complexity, and one of my concerns with the current dialogue between the FDA and laboratories developing LDTs is that quality means very different things to the stakeholders".

Research and Development firms stressed the importance of laboratories outside of manufacture to be held to the same regulatory oversight and stated that a major cause of the inaccuracies of laboratory test development is improper design and lack of validation to verify the result is as intended. This topic was substantiated by consistent feedback mentioned 12 times from all nine interviewees also expressing test validation concerns. Liz Lison, president of Advocea Consulting firm (2015) and a conference speaker explained, "Most of the failures that I have seen in LDTs may have been averted if design controls had been in place. Therefore, I urge the agency not to delay the enforcement of design controls for high-risk tests and potentially introduce a two -tier system for pre-market review." [39]

The oversight of laboratory testing remains with CLIA. However, a gap exists regarding the regulation of test development. Due to the advances in genomic medicine the interviewees expressed that the oversight by CLIA is no longer adequate to manage the compliance needs of laboratories. There is a significant difference in the oversight of the FDA and CLIA. The FDA does not mandate the operation of testing as stated in CFR 493; CLIA does not ensure the safety and effectiveness of test protocols as described in 21 CFR 820 [41]

Results

Secondary Data

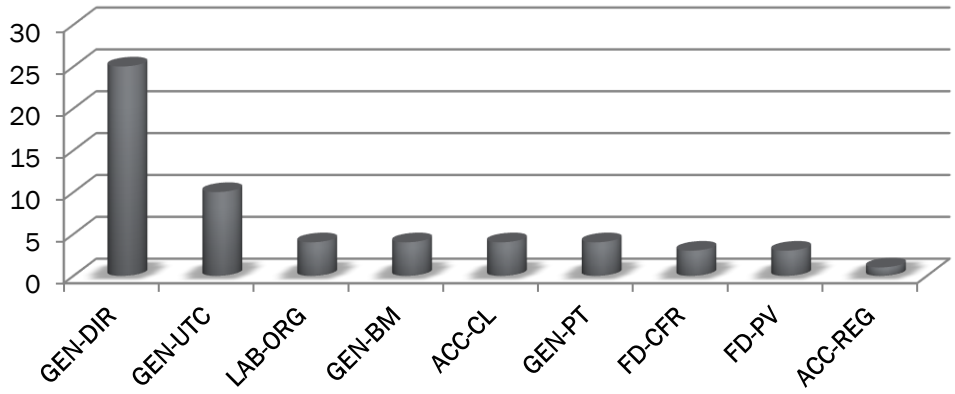


Figure 4: Secondary Data Results

Interpretation of Findings

The interview and secondary findings validated the motivation for this study. The laboratory professionals illustrated the struggle to understand how to develop and organize a framework adaptable to their organization. The participant response from the 2-day work shop was more directive and outlined the need of laboratories versus the uncertainty noted during the interviews. As a result, the participants substantiated the need for a regulatory vocabulary translated to operational laboratory terms. In addition, the feedback describing gaps in processing was instrumental to the development of strategic factors developed from interview and workshop

feedback and proposed as the precursor to a quality systems framework that would serve as the foundation for LDT development as depicted in Table 8:

Table 8: Suggested strategic factors necessary for a regulatory QMS framework [44]

Topic	Interview/Conference Discussion	Strategic Factors developed as a result of the interviews
Interview Topic	Leaders are unclear regarding how 21 CFR 820 requirements applies to laboratory testing considered by many to be a service, not a product.	Leadership Commitment
Interview Topic	Laboratories lacked the rigor that is present in the manufacture of medical devices.	Training
FDA Public Workshop	It is essential that FDA harmonize the QSR requirements with CLIA requirements at a more granular level to prevent duplicate efforts and to ease the regulatory burden" because governmental agencies have not provided the necessary guidance for struggling laboratories	Pre-assessment of the existing Quality Management System
FDA Public Workshop	Laboratory failures due to lack of process control	Design control
FDA Public Workshop	Change is necessary to raise the level of quality, prioritize tasks and dedicate the time and resources necessary to understand regulatory requirements in order to attain process standardization.	Document control

Interview Topic	The major cause of the inaccuracies of laboratory test development is improper design and lack of validation to verify the result is as intended.	Process control
FDA Public Workshop	Laboratories need a guidance documents and a defined process to simplify and translate FDA proposal	Development of a QMS framework
Interview Topic	The importance of test systems to validate protocols, processes and test development that will consistently ensure the effectiveness and accuracy of test results	Process Validation

Survey Results

Exploratory Factor Analysis and Factor Reliability

The factor analysis was conducted to explore the data set, determine the importance of the relationships between the variables and isolate the factors with high loadings to reduce variables into a smaller set of factors. As described by (Williams, et al, 2010) an appropriate factor load of 0.50 is optimal for factor analysis. However, due to the smaller sample size a significant factor loading would be 0.60 or larger. [40] The analysis eliminated 17 variables with smaller loadings as shown in Table 9. The loadings analyzed and clustered the relationships into patterns. The clusters illustrated the importance of leadership, clinical validity, process validation, and procedures to provide guidance for accuracy and consistency of processes. The weak factors removed clarified the reluctance to perform a pre-assessment of the existing operation to determine if the organization was prepared to operate within a regulatory environment.

Table 9: Exploratory Factor Analysis and Factor Reliability performed on each category

Rotated Component Matrix[a]

Statement	Statement Description	Component 1	2	3	4	5	6	7	8	9
Q2_4	Staff training	0.822								
Q3_3	Crosswalk of current processes	0.772								
Q3_5	Clear understanding of QSR requirements	0.701								
Q2_5	The assignment of responsible persons	0.691								
Q7_3	Pre-assessment of current processes	0.635								
Q5_4	Documentation of tasks and activities at each step	0.626								
Q2_3	The program includes value stream mapping to demonstrate the significance of handoffs	0.614								
Q3_2	ISO 15189 will assist the organization comply to requirements	0.612								
Q7_4										
Q7_5										

Q6_4	Clinical validity is performed as validation	0.811							
Q6_3	Documentation of analytic validity will demonstrate accuracy and reliability	0.765							
Q6_1	Responsibility for every handoff to ensure LDT accuracy	0.615							
Q1_3									
Q5_5									
Q8_3	Process qualification ensures design specification		0.871						
Q8_2	Validation to ensure all steps meet regulatory requirements		0.779						
Q8_4	Operational qualification will ensure the process is operating as intended		0.675						
Q7_1									

Q5_2	Clearly written procedures remove ambiguity in the process			0.859					
Q5_1	Updated and accurate operating procedures			0.761					
Q1_4									
Q3_1									
Q8_5	Performance qualification produces the same result and operates correctly				0.696				
Q2_1	Training includes introduction to LDTs				0.659				
Q8_1	Process validation is performed to ensure effectiveness				0.626				
Q2_2									
Q1_2									
Q4_3	Design control well implemented and documented will ensure quality					0.759			

Q4_2	Design control described in laboratory terms will clarify requirements					0.724			
Q7_2									
Q4_4									
Q6_5	Data collection and clearly communicating requirements						0.863		
Q6_2	The consistent uninterrupted flow of material will demonstrate user friendliness of the framework						0.764		
Q5_3									
Q1_1	Leadership institutes key performance indicators							0.699	
Q4_5	A procedure that address adverse events							0.665	
Q3_4									
Q4_1									

Q1_5	Leadership consistently communicate change								0.734

Extraction Method: Principal Component Analysis. Rotation Method: Varimax with Kaiser Normalization.

a. Rotation converged in 15 iterations.

Over all Mean of Categories

To determine if factors were viewed differently by experts versus non-experts the aggregate mean for the items associated with each factor was analyzed. As sown in Table 10, experts versus non-experts chose similar responses for all statements within the survey from an average of close to one – extremely important to slightly over two- very important. This result suggests both groups considered all factors to be equally important for the development of a QMS. (Appendix. VII)

Table 10: Over all Mean of Factors

Descriptive Statistics

	N	Range	Minimum	Maximum	Mean	Std. Deviation	Variance
AverQ3_Preassess	33	2.40	1.00	3.40	1.9515	0.58101	0.338
AverQ4_DesignContrl	33	2.20	1.00	3.20	1.9455	0.60472	0.366
AverQ5_DocuentContrl	33	2.00	1.00	3.00	1.9030	0.58335	0.340
AverQ7_Development	32	1.80	1.00	2.80	1.8844	0.42435	0.180
AverQ6_ProcesContrl	32	1.60	1.00	2.60	1.8453	0.45497	0.207
AverQ2_training	33	1.40	1.00	2.40	1.8364	0.40452	0.164
AverQ8_ProcessValid	33	1.80	1.00	2.80	1.7212	0.48718	0.237
AverQ1_Leadership	33	1.20	1.00	2.20	1.5333	0.32275	0.104
Valid N (listwise)	32						

T-Test Factor Analysis

As shown in Table 11, the mean responses to the factors by experts versus non- experts. The hypothesis was experts and non-experts had different and distinct priorities regarding adoption of a QMS due to their roles and responsibilities within organization and may have answered

statements differently. We found that there was no significant difference between experts and those of non-experts on average importance attributed to the strategic factors**.**

Findings: No significant difference between the responses of experts and non- experts.

Table 11: T-Test Results

Independent Samples Test										
		Equality of Variances		t-test for Equality of Means						
									of the Difference	
		F	Sig.	t	df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
AverQ1_Leadership	Equal variances assumed	1.026	0.321	-0.258	25	0.798	-0.03333	0.12910	-0.29922	0.23255
	Equal variances not assumed			-0.280	19.907	0.783	-0.03333	0.11921	-0.28208	0.21542
AverQ2_training	Equal variances assumed	0.082	0.777	0.543	25	0.592	0.08889	0.16366	-0.24818	0.42596
	Equal variances not assumed			0.572	18.466	0.574	0.08889	0.15549	-0.23718	0.41496
AverQ3_Preassess	Equal variances assumed	0.032	0.859	0.504	25	0.619	0.12222	0.24273	-0.37769	0.62214
	Equal variances not assumed			0.528	18.308	0.604	0.12222	0.23135	-0.36324	0.60768
AverQ4_DesignContrl	Equal variances assumed	0.293	0.593	-0.946	25	0.353	-0.24444	0.25843	-0.77669	0.28780
	Equal variances not assumed			-0.886	13.663	0.391	-0.24444	0.27581	-0.83737	0.34848
AverQ5_DocuentContrl	Equal variances assumed	0.928	0.345	-0.828	25	0.415	-0.20000	0.24148	-0.69733	0.29733
	Equal variances not assumed			-0.893	19.659	0.383	-0.20000	0.22406	-0.66790	0.26790
AverQ6_ProcesContrl	Equal variances assumed	1.221	0.280	0.088	24	0.931	0.01667	0.18916	-0.37374	0.40708
	Equal variances not assumed			0.100	18.558	0.921	0.01667	0.16651	-0.33240	0.36574
AverQ7_Development	Equal variances assumed	0.003	0.958	-0.310	24	0.759	-0.05556	0.17922	-0.42545	0.31434
	Equal variances not assumed			-0.327	15.388	0.748	-0.05556	0.16980	-0.41669	0.30558
AverQ8_ProcessValid	Equal variances assumed	0.901	0.352	-0.272	25	0.788	-0.05556	0.20443	-0.47659	0.36548
	Equal variances not assumed			-0.244	12.335	0.812	-0.05556	0.22808	-0.55100	0.43989

Survey Results: Expert Response per Quartile

The survey results for the most important rated statements with corresponding means as depicted in Figure 5. begins with Leadership Commitment as described for statements, one, two, three and five. (Appendix F.) The commitment of leadership to institute key performance

indicators, direct regulatory initiatives and maintain and consistently communicate change in the organization was considered significant. However, a poorly rated statement was the task of an organizational pre- assessment to determine missing processes, lack of procedures, deficiencies and create a list of necessary guidance documents to comply to regulatory requirements. This outcome was unanticipated due to laboratory accreditation agency practices of a cross walk between laboratory current processes in comparison to requirements. Statements depicting design control were not considered extremely important with all five statements located on the second, third, and fourth quartile, despite the proposal for QSR by the FDA. There were no significant results for the following statements: 1) the statement suggesting a procedure to address the process for identification, documentation and reporting of an adverse event in the laboratory and the 2) establishment of an LDT quality committee to quickly approval changes and provide support.

Respondent Feedback

The open -ended questions presented to the survey respondents in Q9, Do you agree with the strategic factors identified in the proposed framework for Quality Management System of LDTs? If not, please suggest additional factors pertinent to develop a robust framework. This question resulted in positive feedback for the development of a QMS framework and 20 of 35 participants agreed with the strategic factors proposed by the researcher. The respondents agreed that all the factors and statements listed were indeed important. However, leadership buy in was considered imperative for implementation and to ensure the proper resources to address development of the QMS.

	Q1 Leadership Commitment	Q2 Training	Q3 Pre assessment of exsisting QMS	Q4 Design Control	Q5 Document Control	Q6 Process Control	Q7 Development of QMS Framework	Q8 Process Validation	
Mean	Statement								
1.28	Q1_5								Q1
1.3	Q1_1								
1.33	Q1_2								
1.39	Q1_3								
1.44						Q6_4			
1.5								Q8_3	
1.56							Q7_1	Q8_2	
1.61		Q2_2			Q5_5	Q6_3			Q2
1.67				Q4_3				Q8_1	
1.67								Q8_4	
1.71							Q7_5		
1.72			Q3_5	Q4_1	Q5_1				
1.78					Q5_2			Q8_5	
1.82						Q6_1			Q3
1.83		Q2_5					Q7_3		
1.89			Q3_2	Q4_2			Q7_2		
1.89				Q4_4					
1.94		Q2_1	Q3_1		Q5_4				
2		Q2_4				Q6_5	Q7_4		Q4
2.06	Q1_4	Q2_3			Q5_3	Q6_2			
2.17			Q3_3						
2.22			Q3_4						
2.28				Q4_5					

Figure 5: Quartile split of Survey Statements by Expert Participants

Feedback- The Establishment of a Quality Management System Framework

The question presented to the survey respondents in Q10 - Do you think the establishment of a Quality Management System framework will assist LDT laboratories incorporate regulatory requirements such as design control more readily? If not, why and what else is necessary? Out of 35 respondents 23 answered this question with yes, I agree and strongly agree and nine of 35 respondents scripted favorable feedback. The respondents agreed that a fully functional QMS is needed to meet accreditation requirements and document control is critical in this process. An accepted framework will provide the laboratory community "structure, uniformity and integrity" (survey respondent) and the documentation discipline for all laboratories. The process is not only beneficial for the development of LDT but in the general lab as well to comply with accreditation requirements. A crosswalk of each clause of Part 21 CFR 820 can be performed in comparison to the elements of each QSE. The QSE can be used as the QMS framework; however, the most

difficult topic discussed in the draft guidance is clinical significance and how the results derived from a LDT are being used or will be used to guide therapy.

Discussion

The impetus for change within the laboratory community began with the awareness of patients that were adversely affected by the results of a Laboratory Developed Tests. Historically the design and development of LDTs was not under the jurisdiction of CLIA and testing operations are formally not within the oversight of the FDA. Many articulated the FDA has no jurisdiction over LDTs. In addition, before synergistic legislation can occur the agencies must bridge the gap between required regulations. Shelia Walcoff of Goldbug Strategies (2015) and a FDA Work Shop speaker stated that "It is essential that FDA harmonize the QSR requirements with CLIA requirements at a more granular level to prevent duplicate efforts and to ease the regulatory burden" because governmental agencies have not provided the necessary guidance for struggling laboratories. [39] The adoption of a laboratory structure that would satisfy accreditation and regulation requirements in the event the 2014 draft guidance becomes a policy is perplexing. The interviewees expressed that laboratories may be required to change business strategies, outsource or terminate many of the current tests if the FDA proposal becomes a policy.

However, interviewees also expressed that laboratory leaders are taking the wait-and-see approach because the laboratory community considers test development a service, not a product. The interviewees shared their concerns for CLIA and the FDA to collectively develop standards and guidance documents prior to a policy release. The current regulations for medical device include requirements for design control geared for product development and the meaning of design control, methodology and the translation of these regulations from the medical device industry to a clinical laboratory do not exist. The survey respondents agreed that a regulatory oriented

framework for the development of LDTs is needed in the laboratory and it is interesting to note that the survey respondents did not consider design control as extremely or very important despite the proposal for a QSR by the FDA. These findings support the conclusion of ambiguity interpreting the meaning of design control and how this requirement would be adapted to the laboratory environment. Liz Lison, president of Advocea Consulting firm (2015) and a FDA Work Shop speaker explained, "Most of the failures that I have seen in LDTs may have been averted if design controls had been in place. [39]

The eight suggested strategic factors and 40 statements derived from the literature, qualitative interviews and the FDA work shop provide the impetus for design of an QMS. The respondents agreed with all statements relevant to the design of a QMS based on needs and gaps expressed by laboratory professionals. This finding aligns with the results of the survey as there was no significant difference in the way the experts verse non- experts responded to factors and associated statements. All respondents chose statements as 1) extremely important or 2) very important. This finding directly aligns with the recommendation by Katherine Tynan, an independent regulatory consultant from the 2015 FDA workshop that offered advice to governmental agencies as follows:

1. "Develop a common vocabulary that laboratories can understand"
2. "Simplify the cumbersome QSR and assist laboratories translate the directives"
3. "Develop a "QSR fit for purpose and harmonize the standard"

Tynan's advice to laboratories was to "invest in a quality management system, implement all factors of design control, and be proactive and prepare for future regulatory requirements." [39]

Consequently, the preparation of a QMS require the understanding of where gaps exist to develop appropriate processes that would to adhere to requirements. Moreover, this survey

statement suggesting review of current policies and procedures to identify gaps was not considered important by all groups. This was an interesting conclusion because this is general practice within laboratory accreditation agencies.

The future research includes design of an agile, robust quality management system that will incorporate the suggested factors as follows: leadership commitment, training, pre-assessment, design control, document control and development of a QMS framework.

CHAPTER 4. DESIGNING A REGULATORY AGILE QUALITY MANAGEMENT SYSTEM FOR DEVELOPMENT OF LABORATORY DEVELOPED TESTS

Change will not come if we wait for some other person or some other time. We are the ones we've been waiting for. We are the change that we seek. -Barack Obama

Overview

This chapter continues the call for action by assisting leaders to prepare for a regulatory QMS. We address the concerns of the laboratory community and discuss the current position of regulatory agencies. Our premise is to prepare, because this issue holds the likelihood to effect patient safety and as expected, may not go away. We provide step by step instruction to design a QMS. This manuscript was sent for publication in the American Journal of Clinical Pathologists.

Introduction

The position of the Federal Drug Administration (FDA) for the oversight of laboratory developed tests has evolved since the issued 2014 draft guidance entitled *Framework for Regulatory Oversight of Laboratory Developed Tests.*[2] This 2014 draft guidance proposing oversight for laboratories that manufacture in house LDT was fully supported by physicians, pharmaceutical firms, IVD manufactures and insurers, however, received significant objection and opposing public opinion by the laboratory community.[42] To neutralize public opinion, the FDA published a discussion paper dated January 13, 2017 and some claim the oversight by the FDA may be on hold, however, Gatter, (2017) has stated "it is unlikely that the issue is over". [42] In fact, in a January 13, 2017 discussion paper the FDA indicates support for CLIA requirements regardless of the dissimilarity to 21 CFR 820 Quality System Regulation (QSR) requirements. The paper describes three QSR recommendations "consistent with the approach described in the discussion paper" [6] for laboratories that develop LDTs. These quality system regulations address

requirements for test development not mandated by CLIA regulations: These requirements include:

1. *Design Control* – "an interrelated set of practices and procedures that are incorporated into the design and development process, i.e., a system of checks and balances and make systematic assessment of the design an integral part of development" [5]
2. *Acceptance Activities* – "adherence to requirements through inspections, assessments, or other verification" [41]
3. *Corrective and Preventative Action* – The process to investigate the cause of occurrences in the lab to ensure documentation, correction and follow up is performed.[41]

This recommendation, if implemented will constitute a proactive approach to process standardization and compliance to the adoption of a QSR framework. However, many laboratorians are unclear "how to" interpret, extrapolate, design and implement a QSR and the instruction has not been provided. In addition, laboratories are unclear how the framework written from a medical device perspective can relate to diagnostic laboratories. [44] Furthermore, to the 12 Quality system essentials, the nonexistence of a template, guidance document or standard approach to development of a quality management system (QMS) aligned with accreditation requirements, has resulted in "various levels of quality" within laboratories.[12] Laboratories resort to reinventing the wheel or adopt practices aligned with process standardization such as the implementation of ISO 9001, ISO 17025 and ISO 15189 specific to medical laboratories.[12] Although, these documents provide guidance, the successful implementation of process standardization is based on the support of leaders to own and drive an organic, directed initiative with tasks and activities applied to local specific organizational processes. The standardization of successful organic processes can be found described in an early interpretation of a Deming management philosophy,

known as Total Quality Management (TQM). Systematic standardization, top leadership commitment and continuous improvement throughout the entire organization was at the heart of the successful application of Deming management principles as applied to the Toyota Motor Corp.[35] However, it was noted that many laboratory leaders are taking the wait and see approach to implementation of a standardized process that would embark on a framework in preparation for QSR requirements.[44]

Contribution: In this paper, we continue the call for action for proactive leadership commitment to prepare for regulatory requirements for laboratories that develop LDT. We propose the design of a regulatory QMS framework, bridge the gap and illustrate expansion of the 12 QSE to include the factors identified by a previous survey deemed to be optimal for a robust QMS. [44] To avoid duplication, we clarify, translate and integrate pertinent 21 CFR 820 design Control from the medical device industry to the diagnostic laboratory framework.[1] Finally, we illustrate and propose expedited test development with the customization of an agile stage gate hybrid methodology from product development to the laboratory.

Prior Research Findings

In our prior LDT publication, we reported results of a study to explore the concerns of the laboratory community specific to the quality system regulations described in the 2014 draft guidance. [44] The aim was to understand if compliance was possible, and if not, why and what would be the limiting step. The interview responses obtained from laboratory professionals with significant expertise in the field of LDTs expressed ambiguity regarding the FDA draft guidance and questioned the meaning and adaptability of design control. In addition, they were unclear how the requirement proposed by the FDA in the Quality System Regulation in general would translate to the laboratory environment. The opinion of the professional interviewees expressed that

laboratories offer a service, not a product and the QSR does not equate to the laboratory environment.[1] The 2015 FDA Workshop on Laboratory Developed Tests (Jan 8-9, 2015) also included speakers offering direction and encouragement to the FDA to oversee the process of LDTs for patient safety and offered advice for laboratories to begin to prepare.[39]

The authors explored the FDA regulatory requirements described in 21 CFR 820, defined and clarified the terms and compared the directives to the 12 Quality System Essentials as recommended by the CLSI. As we researched the translation of medical device requirements to laboratories, we found commonalities in the manufacturing factors, however, we further identified unaddressed gaps. As the result of qualitative interviews, literature searches and survey feedback, eight strategic factors and 40 supporting statements were developed that addressed the gaps and needs of laboratories. We tested the factors using a survey instrument for functionality, usefulness and agility and all 35 participants agreed that the strategic factors were optimal for development of a Quality Management System (QMS) regulatory framework. The survey respondents agreed with the importance of leadership commitment for LDT, however, the results of the interviewees yielded leaders that are taking the wait and see approach as opposed to being proactive.

What is a Quality Management System?

A Quality Management System (QMS) is "an integrated framework through which organizations systematically define quality objectives linked to their broader strategic goals and develop and implement foundations, organizational structures and processes to achieve these objectives." [45]

The primary and most important step in the design of an integrated framework for QMS is the need for a clear understanding of the terms and definitions of regulatory requirements pertinent to the operation. In addition, Luzack (2012) describes the most important factor to be leadership

commitment to dedicate the time and resources necessary to develop the documents within the QMS that will direct and control all other activities.[46] A significant benefit of a QMS is the adherence to the strategic goals by horizontal control and shared roles across the entire organization responsible for quality. As stated by Meeker *et al*. (2015), an integrated and flexible QMS framework would proactively and strategically prevent and/or reduce risks in quality; a significant benefit for the patient. [45]

Material and Methods

Designing a Quality Management System

The design of a Quality System Regulation (QSR) or a Quality Management System (QMS) is proposed based on six steps as depicted in Table 12. and are further described below (note that terms QSR and QMS are used interchangeably in this text).

Table 12: Steps to Create a Quality Management System

Step	Method
1	Understand the requirements
2	Cross reference the existing 12 Quality System Essentials to match the common 21 CFR 820 clauses
3	Perform an initial assessment to determine current laboratory policies, procedures and processes
4	Develop and implement policies, procedures, processes that describe direction for each requirement
5	Implement tasks associated with stage gate, agile hybrid methodology and assign a responsible person(s) to perform a formal go/no go decision at each handoff of design controls

6	Develop a Quality Management System framework to include all the above

Step 1: Understand the Requirements

The initial step to developing a regulatory QMS is to understand the regulatory requirements as they relate to the context of a particular organization. In addition, mission and vision statements will provide insight regarding the nature of operations—forensic, high complexity, high risk/ low risk, rare diseases, and LDT types.

Step 2: Cross Reference the QSE to the QSR

The elements covered by the 12 QSE and the clauses in the QSR are listed in Table 13. The QSE contain most of the broad management categories included in the 21 CFR 820. The majority of the 12 QSE's should already exist in some form in many laboratories; however, the extent of laboratory application may differ. [24] For each QSE depicted in Table 13, identify the QSR on the right that most closely adheres to the activities in that QSE management principle. Identify any outliers or unaddressed clauses. For example:

1. (QSE) Organization: (management oversight) = (CFR) Management Responsibility
2. (QSE) Occurrence Management = (CFR) Nonconforming product + Corrective/Preventive Actions

To further clarify requirements, Table 14. depicts a cross reference of QSEs and QSRs and lists many of the common activities associated with requirements for laboratory accreditation.

Table 13: The 12 QSE and 21 CFR 820 requirements

12 Quality System Essentials (QSE)	CFR 820 Quality System Regulation (QSR)
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

Step 3: Perform the Initial Assessment

The next step is an initial laboratory assessment to help laboratory leaders identify areas that may lack adherence to regulatory requirements. This assessment will compare current laboratory processes and guidance documents to QSE and CFR requirements. In the CFR, required documents are denoted by the word *shall* in the clause. Existing documents should align to those required by the QSE and QSR. The initial assessment includes, but is not limited to the descriptions in Table 14.

Table 14: QSE and QSR requirements [24,41]

Quality System Requirements (QSR)	**CLSI QMS-01 Quality System Essentials (QSE)**	**Activities for Compliance**	
Subpart B, Quality System Requirements (CFR)	Management responsibility	Quality policy Organization Management review	Quality planning Quality system procedures
	Quality audits Personnel		
Subpart C, Design Controls	Design controls	Classification rules Design and development planning Design input Design output Design review	Design verification Design validation Design transfer Design changes 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	

		Purchasing data	
Subpart F, Identification and Traceability	Identification Traceability		
Subpart G, Production and Process Controls	Production and process controls	Overall requirements Production and process change Environmental controls Personnel Contamination control Control of inspection, measuring, and test equipment Calibration	Buildings Equipment Manufacturing material Automated processes
	Process validation	Validation requirements Review effect of process changes and revalidate	Procedures for monitoring validated processes
Subpart H, Acceptance Activities	Receiving, in-process, and finished device acceptance	General requirements Receiving acceptance activities	Final acceptance activities Acceptance records

		In-process acceptance activities	
	Acceptance status		
Subpart I, Nonconforming Product	Nonconforming product	Control of nonconforming product Nonconforming review and disposition	
Subpart J, Corrective and Preventive Action	Corrective and preventive action	Procedures for corrective and preventive action Activities and results must be documented	
Subpart K, Labeling and Packaging Control	Device Labeling	Label integrity Labeling inspection Labeling storage	Labeling operations Control number
	Device Packaging		
Subpart L, Handling, Storage, Distribution, and Installation	Handling		
	Storage	Procedures for control of storage areas and stock rooms Procedures that describe methods that	

		receipt from and dispatch to storage and stock areas	
	Distribution	Procedures for control and distribution of finished devices Distribution records	
	Installation	Installation and inspection instructions Insure proper installation, and document inspection and test results	
Subpart M, Records	General requirements	Confidentiality Record retention period Exceptions - what records do not need to be provided to FDA and what can be presented instead	
	Device master record	Device specifications	Packaging and labeling specifications

	Production process specifications Quality assurance procedures and specifications	Installation, maintenance, and service procedures
Device history record	Dates of manufacture Quantity manufactured Quantity released Acceptance records	Primary identification label(s) Any device identification(s) and control number(s) used
Quality system record	Have procedures for and maintain complaint files	
Complaint files	Review and evaluate all complaints Investigation of complaints relating to device failure, labeling, or packaging	Maintain records of investigations Records of investigations must be reasonably accessible to the manufacturing establishment

		Review, evaluation, and investigation of reportable events	If complaint unit is outside of US, records must be accessible with the US
Subpart N, Servicing	Servicing	Where servicing is a requirement, procedures are required Analyze service reports	Any service report that represents a reportable event shall be considered a complaint and processed accordingly Structure of service report
Subpart O, Statistical Techniques	Statistical techniques	Where appropriate, procedures for valid statistical techniques Sampling plans, if used, based on valid statistical rationale	

Appendix D. contains an assessment checklist that can be used to document existing laboratory processes in comparison to the elements of the standard that may need to be addressed.

Laboratories may not perform all manufacturing processes described within each specific requirement listed in 21 CFR 820. The following exception found in Subpart A, General Provisions

Scope provides justification as follows: “if a manufacturer engages in only some operations subject to the requirements in this part, and not in others, the manufacturer need only comply with those requirements applicable to the operations in which it is engages”. [41] Note: the exclusion of activities associated with clauses in the 21 CFR 820 requires rationale to omit and documentation recorded in the quality manual. In addition to the operational requirements listed above, the elements addressing design, manufacture, testing and approval of LDTs have historically not been included in the original 12 QSE.

The requirements identified in Table 13 and the results of the initial assessment documented on the assessment form in Appendix D. will provide insight into the elements needed to craft a comprehensive quality framework. The final framework, integrated with QSE and the QSR, is depicted in Figure 6.

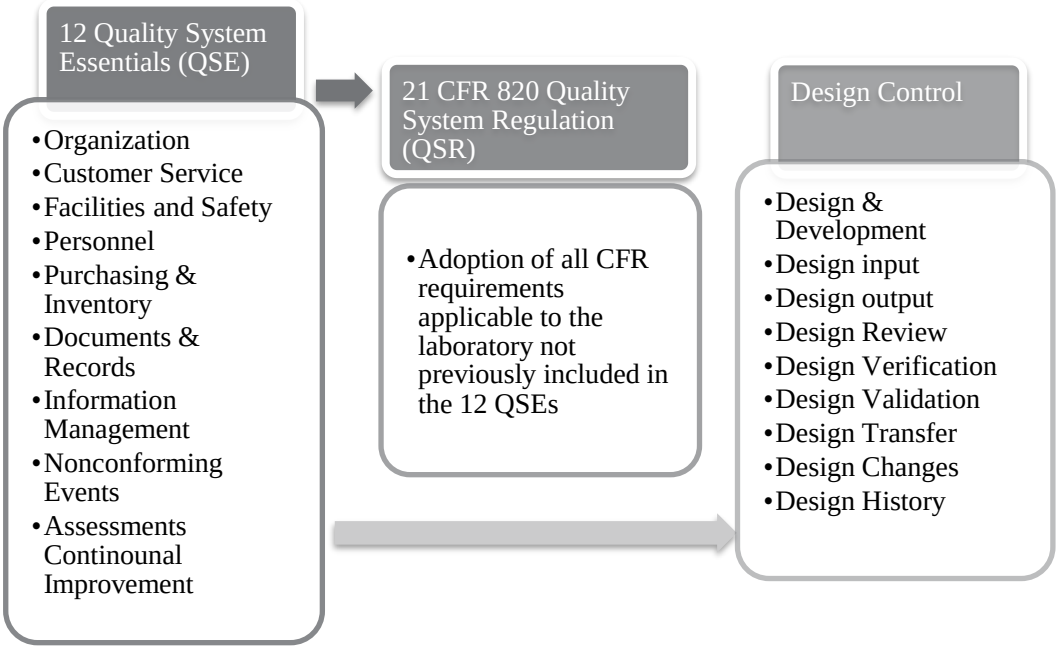


Figure 6: The 12 QSE integrated with 21 CFR 820 requirements

Step 4: Develop and Implement Policies, Procedures, Processes Identified as Missing During Assessment

The process of cross referencing the 12 QSE to the 21 CFR 820 clauses and the results of the assessment will provide an accurate determination of policies, procedures and processes still required to develop a robust QSR. To comply with regulatory requirements, Table 13. represents a high-level guide for the description of activities that must be addressed. For a more comprehensive listing see the 21 CFR 820 Standard.[41] Any existing documents not meeting requirements should be revised and approved using organizational document management protocols.

Step 5: Design Control

The fifth step includes design of a structure to include all elements of design control not previously included in the 12 QSE. The prior assessment step will determine existing laboratory processes that may align with elements of design control. Figure.7 lists each element of Design Control and includes a high-level description for the development of pertinent laboratory guidance documents. The laboratory shall develop of policies, procedures and processes as applied to test design to ensure requirements specific to the laboratory are met and proper documentation is maintained. Consistent documentation of all tasks and activities throughout each stage of development is critical and will capture all changes and modifications as discussed in Design history.

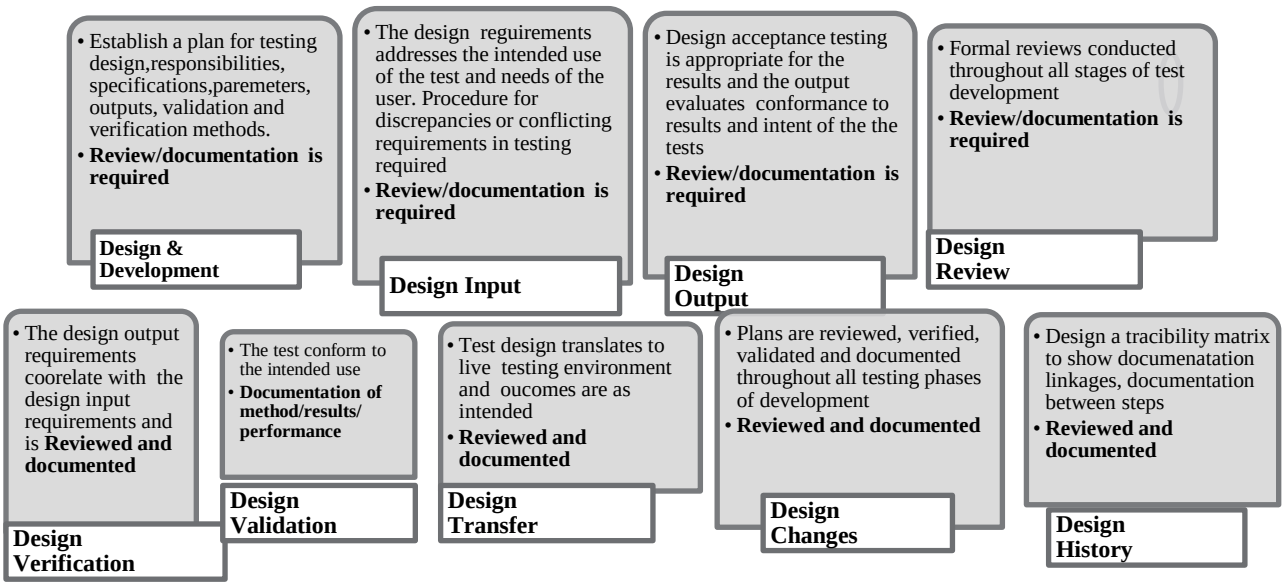


Figure 7: Elements of Design Control for LDTs (21CFR 820) [29]

Step 6: Establishing an Agile Stage Gate Methodology

To expedite the development of LDTs and ensure all steps are well reviewed and documented, the framework may be further established by the use of a product development methodology called Agile Stage Gate Hybrid. The agile methodology was initially established for the speedy development of new software codes by IT leaders and currently are used in other industries with high risk, proliferation costs and limited life cycles such as high tech and product development. An Agile product development methodology differs from traditional (PD) due to just-in-time internal/external communication and feedback to document and expedite change. The traditional Stage Gate technique as described by Cooper (2008) consist of an initiative or project (e.g., new product development, software development, process improvement, business change) divided into distinct *stages* or *phases*, separated by decision points (known as *gates*). [47] The Stage Gate process is described as a macroplanning process that begins with the discovery stage or an initial deep understanding of requirements, explained as "camping with the customer".[47] An initial planning meeting is held to define regulations, requirements, ideas, and develop the plan with

strategic goals and productive outcomes. A manager is assigned at discovery to validate and move the test through each gate to the next stage in development. The project then moves through the process of scoping, building a business case, project development, testing, validation and launch with a go or no-go decision at each handoff.

An LDT Launch Executed with Stage Gate Technique

Comparable to typical product development, the LDT process launch begins with the test concept, design and development and the test is classified (Figure 8). Within Stage 2, the design input addresses and verifies the intended use of the test and in Stage 3 clinical validity and the conformance of the acceptance criteria is confirmed. The task of Stage 4 is to verify that the output of the design requirements meet the input criteria and Stage 5 serves to validate the process under defined operating conditions. Stage 6 is the successful transfer of the test design to the live laboratory environment; however, each stage does not advance until the go/no go determination is made. The stage gate responsibilities include the following tasks: 1) Inspection at each phase and 2) Design change, review and history file to document all changes to the process.

A comprehensive review is conducted at post launch to discuss lessons learned and to identify potential challenges for the next launch. This approach to an LDT launch will perpetuate clearly communicated processing information, will expedite the process and allow for just-in-time response and resolution to meet rapidly changing needs. This technique is credited with increased team communication, positive outcomes, just-in-time responsiveness to rapidly changing customer requirements and faster product to market.[16]

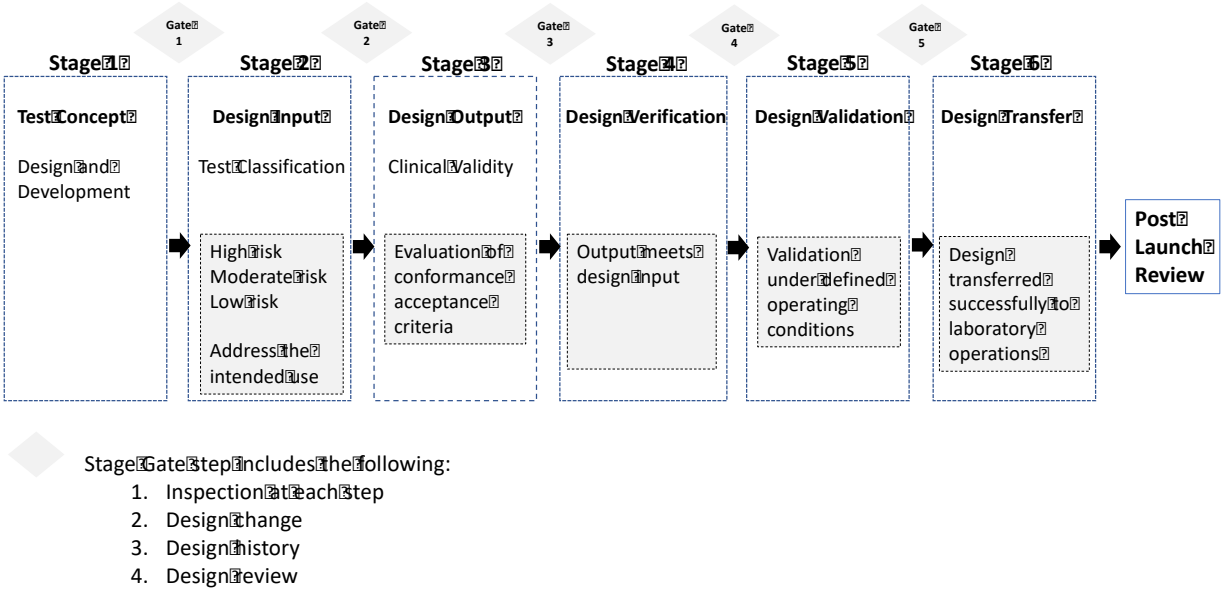


Figure 8: Agile Stage Gate Hybrid Technique adaptable to LDT development [49]

The Application of Agile to Stage Gate

The agile function within the stage gate technique is considered a microplanning process that utilizes a project management (PM) approach within each gate with specific activities and the assignment of dedicated cross-functional teams. Cooper and Sommers (2016) describe that the most successful applications of agile stage gate hybrid methodology come from organizations that assign owners to each gate with the authority to stop the process due to quality concerns.[48] The dedicated teams manage, maintain and own the launch and are responsible to document details and obtain approvals at each gate. In addition, the teams conduct short daily meetings usually 15 minutes in length to accomplish the following: 1) review accomplishments from the prior day, 2) brainstorm resolutions to preexisting discrepancies, 3) prepare for the current day, and 4) review team progress from past assignments.

The technique is further divided using "sprints" (short iterations) to develop the project in short increments or stages usually from one to four weeks. There are three types of agile stage gate hybrid techniques:

1) *Agile and Iterative Development*: This type of application is effective when the process is consumed with uncertainty, change and speed is crucial to success of the project.
2) *Adaptive or Spiral*: This technique employs multiple projects with extended iterations when the process is continuously evolving.
3) *Accelerated*: This technique is optimal when speed is imperative by adapting the following: 1) Application of Lean tools such as value stream mapping to identify processes fraught with waste and inefficiency and 2) Simultaneous execution to allow multiple projects to intersect and advance without the need to remain in one stage until all information has been established.[48]

Regardless of the agile technique employed, the process requires leadership to direct and own the project with the immediate focus on the backlog of issues. The process is iterative and may include cyclical projects simultaneously conducted at each step throughout the entire stage gate (Figure.9). The team evaluates user needs by brainstorming new solutions and aligns the process to accomplish positive outcomes. The new solutions are discussed at the daily or weekly sprint meetings and a review is performed to understand lessons learned, successes, failures, assignments and what's next. The cyclical process continues.

The characteristics of the agile technique for LDT development include:

- Early and continuous customer (FDA) involvement
- An initial comprehensive planning meeting that includes all members of the team

- Training for leaders and team members in the agile stage gate methodology prior to execution
- Empowerment of teams and assignment of responsibility and accountability
- Establishment of the Rules of use: 1) Just in time communication requirements, 2) Discussion of progress/failures, and 3) Consistent documentation at every step.
- Continuous learning
- Documentation and follow up of quality issues associated with the LDT process

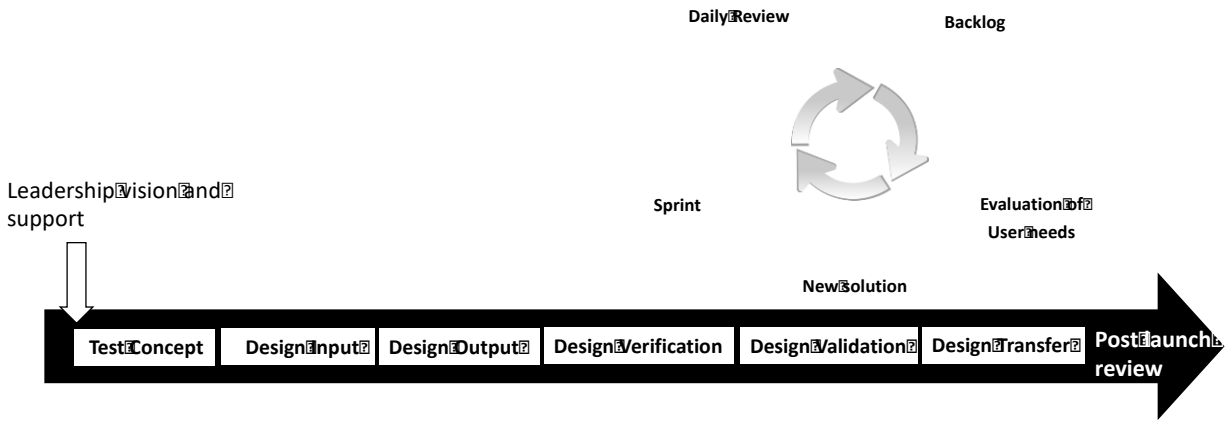


Figure 9: Agile methodology adapted to LDT development [49]

Medical Test Validity

The CLIA regulations require laboratories to establish performance characteristics to validate the accuracy and precision prior to testing patient samples. (42 CFR 493.1253). [50] Clinical and analytical validity should be verified at each step. (Table 15.)

Table 15: Criteria for Medical Tests

Analytical Validity	"Analytical validity defines the ability of a genetic test to measure accurately and reliably the genotype of interest during pre-analytic, analytic and post-

	analytic phases of testing. This part of the evaluation is concerned with assessing test performance in the laboratory as opposed to the clinic". [51] Does the test measure what we say it measures?
Clinical Validity	"Accuracy with which a test can predict the presence or absence of the phenotype or clinical disease". [51] Does the measurement correlate with a clinical situation?

To ensure the clinical validity of a test protocol the following activities and reviews may be performed. [17]

1. Linearity Study
2. Analytical Sensitivity
3. Precision
4. Analytical Specificity
5. Accuracy Comparison of Methods
6. Reference Intervals/cut off points

For more information regarding Clinical Validity, see CLIA regulations website.

Design History

In the stage gate technique, the team lead or process owner is responsible to follow through, resolve issues and document tasks and activities interacted throughout the entire LDT process. The illustrative example matrix depicted in Figure.10 can be used as a management tool to maintain documentation. [29]

NOTE:

Link each entry to file with additional information and data.

Design History File Traceability Matrix

		Design History File Traceability Matrix											
Entry #	Date	User Needs/Regulation	Reviewed by/Date		Design Inputs	Reviewed by/Date		Design Verification	Reviewed by/Date		Design Validation	Reviewed by/Date	
1	1/12/16	Secured Supplier. Performed Supplier Qualification. Ok to use.	RD	1/18/16	New supplier added to list	RD	1/18/16	Performed Supplier performance and monitoring. Supplier continues to be accepted.	RD	1/26/16		DC	1/18/16
2	8/16/16	Testing- allergy Ag	RD	1/16/16	Ordered XYZ Reagent. Manufacture insert stated dilution is stable for 8 hours	RD	1/16/16	Testing/QC check performed on XYZ reagent on 8/14/16. OK to use.	RD	1/18/16		RD	1/20/16
3	1/12/16	MDR	RD	1/18/16	Reportable error	RD	1/18/16		RD	1/26/16		DC	1/18/16
4	8/16/16	Validation	RD	1/16/16	(IP, DP, DP)	RD	1/16/16		RD	1/18/16		RD	1/20/16

Figure 10: A matrix example of required documentation for LDT Design History

Step	Process	Task	Documentation
1	QSE	Develop a policy, procedure and process for each QSE not already addressed	All documents are controlled, readily available and the current version
2	21 CFR 820	Develop a policy, procedure and process for each clause not included in the QSE	All documents are controlled, readily available and the current version
3	Risk Classification	**High risk**: an incorrect result could to lead to serious consequences for the patient. The application for premarket review must be submitted prior to offering the test. **Moderate risk**: an incorrect result may lead to the morbidity, mortality or may compromise the safety of patients. The laboratory must submit validation studies describing accuracy and clinical validity prior to offering the tests for premarket review. **Low risk**: an incorrect result or incorrect interpretation is unlikely to affect morbidity, mortality or safety of patients.	

4	Design Control	Develop a policy, procedure and process for each clause included in the QSR, Design Control	All documents are controlled, readily available and the current version

Step 6: Develop the Quality System

The development of a comprehensive and robust quality management system begins with the adoption of the 12 QSE (Step 1) as explained in Table 16. As stated previously, many laboratories are adopting quality management standards, which (if executed to completion) will prepare the organization for complying with regulatory requirements. Step 2 addresses the establishment of guidance documents for the 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. Listed in Step 4 is the development of policies processes, and procedures specific to each element of design controls. When executed appropriately these documents will allow for a cascade of verification steps from LDT initiation to testing. The series of controlled hand offs will ensure a fail-safe process with quality built into every step. Figure. 11 depicts the Stage Gate process that incorporates all elements of the QSR.

Table 16: Steps to Develop a QMS

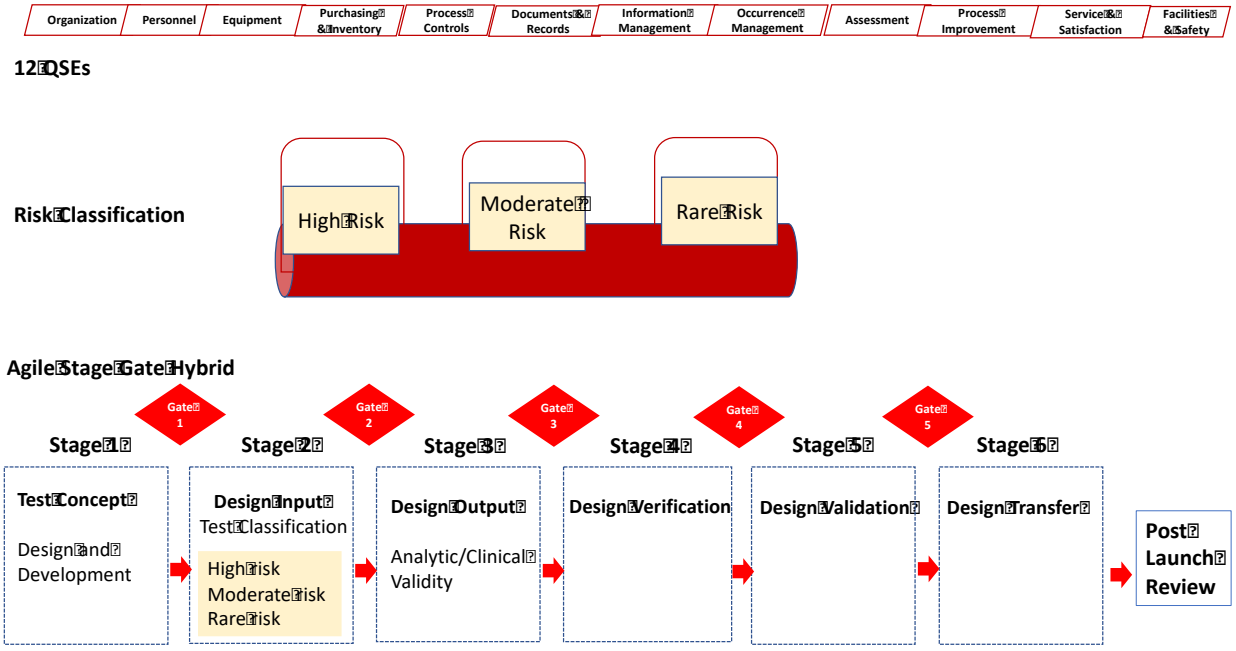


Figure 11: Design of an Agile Stage Gate Hybrid Regulatory Quality Management System

Conclusion

The patient safety concerns identified by the FDA was a turning point in the history of laboratories. Whether one is in support of the FDA draft guidance for a QSR in the laboratory, or against it, we can all agree that a robust quality management system will provide the structure for accuracy and efficacy of LDT design, development and testing, therefore, assuring patient safety. The primary constraint of laboratories is the unfamiliarity of the regulatory standard, the meaning of design control and the application to laboratory medicine. The challenge becomes the adoption of an unfamiliar regulatory requirement and adoption of a formal design control methodology. However, after careful review of existing processes the reader may identify some form of the requirement already in place, but possibly named differently. The existing process can be expanded to incorporate the requirement and the terminology is irrelevant if the guidance

document and process address the regulatory requirement. Documentation of each regulatory task and activity along the path of LDT is key to demonstrate compliance.

CHAPTER 5. IMPLEMENTING AN AGILE QUALITY MANAGEMENT SYSTEM FOR DEVELOPMENT OF LABORATORY DEVELOPED TESTS

"An accepted framework throughout our industry will set a level playing field as well as provide structure, uniformity and integrity to the entire LDT process. '" (survey participant)

Overview

This chapter assists leaders develop a regulatory QMS structure that is comprised of six stages of development. The six stages are as follows: 1) establishment of a leadership support structure, 2) training, 3) pre-assessment of current laboratory processes, 4) adoption of design control, 5) process controls, 6) process validation and the application of an agile Stage Gate technique for test development.

Introduction

In 2014, the FDA released a draft guidance for laboratories that develop in-house tests entitled *Framework for Regulatory Oversight of Laboratory Developed Tests (LDT)*. [2] In this draft, the FDA provides guidance for laboratories that manufacture LDT and explains that enforcement discretion once considered optimal for laboratories is no longer appropriate due to the expansion of LDT development. The agency acknowledges the current regulatory gap between CLIA and the FDA. Joshua Sharfstein MD, (2015) asserts that these gaps in the present "regulatory system under CLIA present a public health risk" and, in response, proposes risk classification, timeframes for LDT registration, medical device reporting and a phased approach for implementation of a Quality System Regulation (QSR) for laboratories that register LDT for Pre -Market Approval (PMA) or 510(K) classifications. [3]

Due to differences of opinion within the pathology community, the FDA announced in a Discussion Paper dated January 13, 2017 that a final draft guidance would not be issued to allow

for additional public discussion and a legislative solution. However, the agency continues to support the proposition for regulatory requirements from the 2014 draft guidance and, in a 2017 Discussion Paper [6], underscores the importance of a (QSR) for the development of LDT that includes design controls, acceptance criteria and corrective and preventive action procedures.

In our initial publication, Facing the Inevitable: Being Prepared for Regulatory Requirements for Laboratory Developed Tests, we discuss the prospect of FDA oversight within laboratories. [44] We explore adherence to a QSR as proposed by the FDA, because we believe, as does Gatter, (2017) that "it is unlikely that the issue is over". [44],[42] We also examine the potential implications in the event the FDA gains greater authority over laboratories that develop in house laboratory developed tests. Our goal is to understand the regulatory requirements and to consider the adoptability of the proposal by laboratories, but more importantly to assess the understanding of the community regarding these requirements. The original question that set the path forward for this research was the following: Is compliance to the draft guidance possible, and if not, why not and what are the constraints? [44]

To gain an understanding and to answer this question, we interviewed nine laboratory senior leader professionals with significant knowledge in the field of LDTs. [44]

Their response yielded a significant lack of clarity regarding the FDA draft guidance and substantial disparity regarding the meaning of design control as described in 21 CFR 820. In addition, we found these leaders struggling to understand how design control could be adapted to the diagnostic laboratory since the 21 CFR 820 uses terms relevant to medical devices, not laboratories. [1] For the respondents, the intent of the FDA proposal is not fully delineated. The most problematic finding from the responses was that the interviewees consider laboratory testing and reporting a "service, not a product" and, by extension, not subject to "design control" regulations.

Based on the interview results and literature searches, we developed eight strategic factors and 40 supporting statements. [44] The strategic factors were tested for functionality, usefulness and agility through a survey instrument. We found 35 survey participants in the field of LDT who agreed with the eight strategic factors relevant for development of a Quality Management System (QMS) regulatory framework. [44] In addition, we collected the top ten supporting statements and associated strategic factors from participants considered experts in the field of LDT and developed our findings into building blocks for a regulatory quality management system specific to laboratories. The collection of this data serves to 1) clarify the needs of laboratories and 2) translate the needs into laboratory terms and operational processes otherwise interpreted by the laboratory community as applying only to medical device requirements. During the interviews for this initial publication, we observed that leaders are taking a wait-and-see approach as opposed to a proactive stance, while advice for laboratories from speakers that attended the 2015 FDA Workshop on Laboratory Developed Tests Jan 8-9, 2015 is that "laboratories must begin to prepare." [39, 44]

In a sequel publication, Designing a Quality Management System for Laboratory Developed Tests we propose translating the above eight strategic factors and 40 statements into a QMS design for LDT oversight that would satisfy the QSR requirements applicable to laboratories. [52] We discuss the comparison between the 12 Quality System Essentials as recommended by the Clinical Laboratory Standards Institute (CLSI) [9] used by many laboratories to the 21 CFR 820 requirements. We demonstrate a process to identify and resolve noted gaps between existing processes and requirements described in the QSR applicable to addressing LDT development in the diagnostic laboratory. [52]

Finally, in this second publication we explain the advantages of an agile stage-gate-hybrid product development methodology successful in other industries as a novel approach to expedite

LDT development. We illustrate the importance of dedicated cross-functional teams with the authority to perform go/no-go approval/rejections at every step and the value in assigning change agents and process owners. In conclusion, we suggest the design for a robust quality management system framework that follows all pertinent regulations. [52]

In this, our third paper, we illustrate the top ten supporting statements and associated factors chosen from experts in the field of LDT, we highlight the findings from participant feedback and we demonstrate the translation of those factors into an QMS implementation plan. This implementation plan consists of operational processes, which can function as an extension of the existing laboratory framework and can be crafted into a regulatory QMS for laboratories. We adopt a proven product development methodology successful in other industries and customize it to a novel approach for LDT development called Agile Stage Gate Hybrid technique. [47]

The contribution to the literature: We provide the rationale to move away from the wait and see approach regarding the adoption of regulatory requirements and we provide an implementation guide for a regulatory QMS with structures that support LDT development. We include a novel approach to LDT oversight by utilizing the Agile Stage Gate technique adapted to the laboratory context which enlists dedicated cross -functional teams to manage and expedite LDT design and development. We also suggest the assignment of change agents/process owners with the accountability and authority to effect go/no-go approvals at every step. [48]

Figure 12: Elements of a quality management system

Prerequisite: A Quality Management System for Laboratories

A Quality Management System (QMS) is a diagnostic laboratory framework defined as "coordinated activities to direct and control an organization with regard to quality". [37] This infrastructure, instituted in many laboratories, consists of the adoption of a set of management standards called the 12 Quality System Essentials (QSE) as recommended by the Clinical Laboratory Standards Institute (CLSI). [24] This systematic approach to quality considered by the World Health Organization as a "path of workflow" begins with the patient and ends with the diagnostic result; however, the depth of implementation varies across laboratories. [37] Consequently, a robust quality structure is only established through the comprehensive development of policies, procedures and processes of each element designed at a local, organic level. (Figure.12) The QMS elements are as follows: [53]

Goals of an QMS Implementation Guide

The goal of this research is to provide guidance for laboratories who wish to extend the existing quality management system structure by adopting and incorporating pertinent QSR clauses into their operational processes to demonstrate a proactive approach to LTD oversight and to assure patient safety.

Materials and Methods

As stated earlier in this text, a QMS framework consists of a comprehensive collection of policies, procedures and processes that address each management standard. In preparation for this implementation guide, we assume that a comprehensive structure consisting of the 12 QSE (Table 17) has been previously implemented and is currently operational in the laboratory. The method for implementing a regulatory QMS is outlined below:

1) description of the strategic factors and supporting statements identified as extremely important for a QMS by experts for LDT development,

2) translation of pertinent interviewee/survey feedback into pertinent operational processes, and

3) implementation plan that describes the six phases of development, in sequential steps, and an action item checklist.

Table 17: CLSI's 12 Quality System Essentials Framework [24]

1. Organization
2. Customer Service
3. Facilities and Safety
4. Personnel
5. Purchasing &Inventory
6. Equipment

7. Process Management
8. Documents and Records
9. Information Management
10. Nonconforming Event Management
11. Assessments
12. Continual Improvement

Using the Strategic Factors as a QMS Development Guide

The top ten out of 40 strategic factors and supporting statements identified as extremely important for a QMS by experts is used as a guide to design, develop, implement and extend the existing laboratory framework to a regulatory QMS for LDT development. In addition, the interview and survey participant feedback serve as rationale for the development of regulatory processes within the implementation plan (all strategic factors and statements from the study are listed in Appendix D. Table 18 lists the selected supporting statements paired with eight associated strategic factors, interviewee feedback and the resulting implementation plan.

Table 18: Supporting statements with associated factors chosen by experts for LDT development feedback and guidance contributing to implementation plan

Strategic Factors	Supporting Statements	Supporting Feedback	Corresponding Implementation Plan Elements
1.Leadership	Statement 1: Leadership institutes key performance indicators that outline, measure and	Leadership provides "buy-in to review and re-evaluate whether current resources (both personnel	Top management commitment, strategic planning,

	direct regulatory initiatives	and equipment) are sufficient to address QMS gaps, maintain established processes, implement change and allow the time necessary for the implementation of this work outside of normal duties."[44]	employee empowerment
	Statement 2: Leadership commitment to initiate and maintain change in the organization		
	Statement 3: The establishment of a QMS includes oversight by a knowledgeable, educated, responsible, informed, cohesive team to effectively manage the process		
	Statement 5: Leadership consistently communicates change		
2. Training	Statement 7: The course material includes regulatory requirements and terms and definitions in alignment with CLIA 88, 12 QSEs, 21 CFR	"Provide laboratories with the tools to ensure LDT development is conducted and documented consistently, with the demonstration of	Understanding of regulatory requirements, terms and definitions

	820/QSR and Design Control	regulatory compliance as a by-product." [44] (survey participant)	
3.*Pre-assessment of c**urrent QMS**	Not on the list of most important	"I do think that you could crosswalk each clause of Part 820 to the elements of each QSE and use the QSEs as the QMS framework for LDTs. (survey participant)	Development of missing policies, processes, procedures, job aids, forms QSE⇔QSR
4.*Design Control	Not on the list of most important	"Design and document control is paramount for a functional QMS." [44] (survey participant). "	Design and development: input, output, review, verification, validation, transfer, changes, history files Adverse event reporting
5.Document Control	Statement 25: A document control system will ensure documents are current and are readily available		
6.Process Control	Statement 29: Clinical validity is performed to validate whether the	"The biggest issue with some of the most complex LDT's is the clinical	Clinical validity; performance characteristics

	design and optimization of the test protocol will yield testing outcomes that can be used to develop a useful clinical intervention.	significance, and how results derived from a LDT are being used or will be used to guide therapy." [44]	
7.Development of a QMS	Statement 31: The primary step to develop a regulatory QMS is to define a leadership support structure with defined roles, responsibilities, and oversight	"A fully functional QMS is needed for a laboratory to meet accreditation requirements." [44]	Agile Stage Gate Hybrid technique to expedite LDT development
8.Process validation	Statement 37: A validation plan includes: Process Qualification, (PQ) Operational Qualification (OQ), and Performance Qualification (PFQ) to verify that all steps in the	"Testing an ample number of samples to substantiate the intended outcome" [44] (Interviewee # 3) Because, validation "is critical to ensure the safety of the patient and should be considered the standard of	Validation PQ, OQ, PFQ

	process meet or exceed regulatory requirements	care. ” [44] (Interviewee # 2).	
	Statement 38: Process Qualification (PQ) ensures the necessary components of the process are implemented according to design specifications. Documents necessary for operation, performance and maintenance are verified and the process includes all pertinent factors		

Note: The strategic factors 3) pre-assessment of the current QMS and 4) design control was not considered extremely important but operationally necessary to identify processes that lack adherence to standards.

Implementation Plan

The implementation plan includes the following:

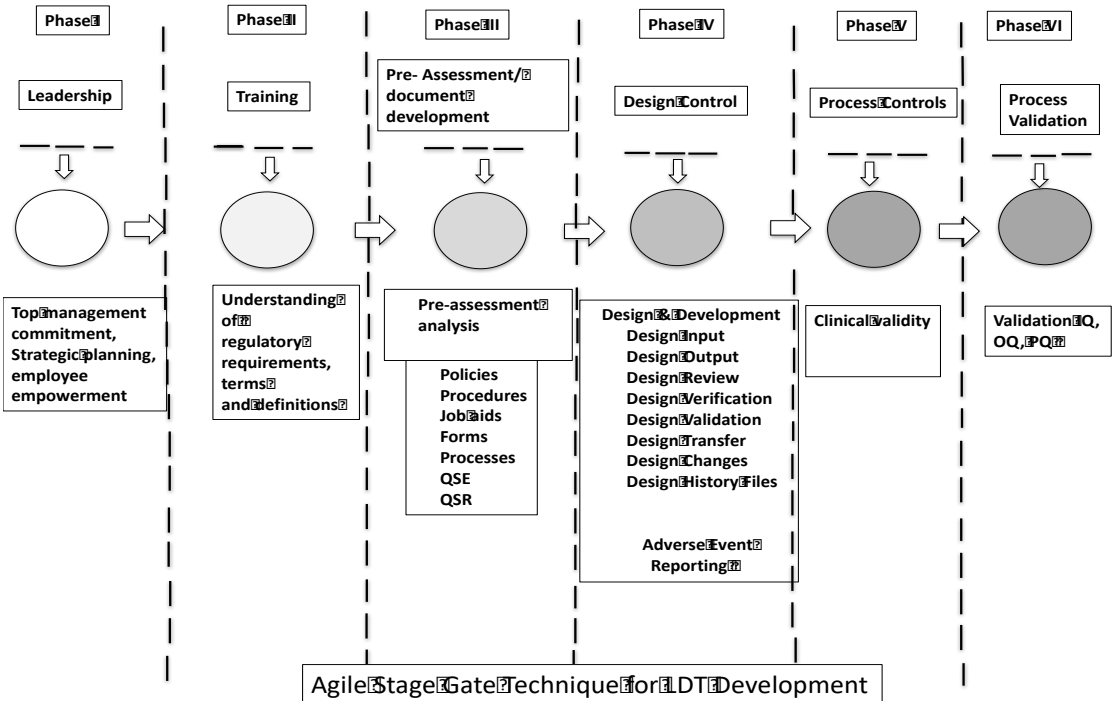


Figure 13: A QMS Implementation Plan consisting of six stages of development

Phase I: Development of the Leadership Support Structure

A leadership support structure provides the necessary resources to direct the initiative, establish leadership oversight at each step throughout LDT development, remove obstacles within the path of workflow, and provide ongoing support. Within this leadership structure, sponsorship and directives are established, change agents are selected, team leaders are assigned, teams are identified and meeting schedules are executed. The establishment of an expeditious pathway from LDT development to FDA approval requires the commitment of leadership to own and direct the initiative and dedicate the necessary resources to plan, develop, execute and communicate all tasks and activities. John Kotter recommends the establishment of a dual operating system that consists of traditional leadership to manage the organization and the recruitment of volunteer change agent leaders through a "strategy accelerator network." [54] This network employs volunteer change agents

as leaders to dedicate sole responsibility for the initiative and assume the responsibility for innovation, change, and strategic initiatives. [54]

In this dual reporting structure, the change agent leadership commits to ensure a quality structure that will sustain the initiative and provide ongoing support. In addition, will dedicate the time to demonstrate accountability and ensure discrepancies within the flow of work are identified, resolved, corrected and documented in real time. The dual reporting structure of leadership support includes the following:

1. Traditional Leadership: Development of a regulatory strategic plan
    a. Development of key performance indicators
2. Change Agent Leadership: Leadership participation, sponsorship and directives
    a. Outline and measure compliance with regulatory initiatives
    b. Participation and demonstrated support
    c. Assignment of roles and responsibilities to every aspect of the QMS framework:
        i. The establishment of a QMS includes oversight by a knowledgeable, educated, empowered, responsible, informed, cohesive team to effectively manage the process.
3. Change Agent Leadership: Continuously communicates through the establishment of a formal structure of change throughout the organization

Directions: Consider John Kotter's dual reporting structure to assign a responsible, dedicated change agent leader for LDT development: [54]

LEADERSHIP ACTION ITEMS: List the following:

1. Develop and communicate a strategic plan goal statement
    a. Example: "The organization will develop and adopt a regulatory quality management system within the next fiscal year."
2. Provide leadership support for creating an LDT structure
3. Establish communication pathways to ensure continuous communication throughout the process
    a. Example:
4. Form an LDT Oversight Team
    a. Leader

Phase II: Training

The training includes understanding regulatory requirements, applicable terms, and definitions, and the importance of documentation throughout the process. In addition, the training program includes forming teams for each segment of the LDT process, assigning leaders and emphasizing the importance of communication. Luzack, (2012) describes staff training as an essential preparatory step in advance of implementation of a QMS because the key to effective implementation is a knowledgeable team with an all-encompassing understanding of requirements. [46] The program outlined includes training modules for the following:

1. What's My Role?
    a. Introduction to LDT development, roles and the assignment of roles, responsibility of leaders and staff "contributing to the success of the quality system". [46]
2. Understanding regulatory guidelines
    a. Regulatory requirements and the understanding of terms and definitions for the alignment of CLIA 88, 12 QSE, 21 CFR 820/QSR and Design Control

3. Document Control to comply with Design Control

    a. Document management is the operating control center of a QMS that provide direction for staff to perform daily tasks and demonstrate objective evidence that the LDT was performed according to policies and procedures. [53] Training for document control and record retention at a minimum should include the following:

        i. New document development, review, approval and retention

        ii. Review and approval of changes

        iii. Documentation/review/approval/retention at every step of LDT development [53]

4. Agile Stage Gate Hybrid Technique

    a. The LDT process is clarified using standard project management tools, such as the Stage Gate technique. [47] This process allows knowledgeable staff the flexibility to expeditiously transport LDT successfully throughout the system, ensuring all changes are well-reviewed, documented, and communicated in real time. The training modules should include an understanding of the Agile Stage Gate Hybrid technique that also include: accountability, ownership for go/no-go decisions at each handoff, conducting short daily meetings or huddles and continuous follow-up to previous tasks.

Direction: Consider constructing the following for implementation of the training program:

TRAINING ACTION ITEMS: List the following:

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

Phase III: Pre-Assessment and Development of Policies, Procedures and Processes

The pre-assessment phase includes a review of policies, processes, and procedures within the existing management structure. This is a critical step commonly performed by agencies for laboratory accreditation and ISO 15189 programs. The assessment performed by these agencies help the laboratory outline the current state and future state of the QMS. The adoption of ISO 15189 international standard for medical competence serves as a system-wide approach to quality and provides guidance to develop, standardize and share a common set of policies, processes, procedures and practices across the entire organization. [45] Adoption of ISO 15189 will prepare the organization to reach a level of quality more consistent with regulatory requirements. As stated earlier in this text, significant variation exists between laboratories; however, laboratory accreditation is on the rise in the US, resulting in higher laboratory quality. According to the College of American Pathologists (CAP) there are 32 laboratories in the USA that have voluntarily earned ISO 15189 accreditation and many pursuing additional quality management standards. [13,38] Table 19. consists of reconfigured management requirements organized

into similar clauses to demonstrate the commonality and alignment between 12 QSE, 21 CFR 820 and ISO 15189.

Table 19: QSE in comparison to the 21 CFR 820 requirements and ISO 15189 requirement

12 Quality System Essentials (QSE)	**21 CFR 820 Quality System Regulation (QSR)**	**ISO 15189:2012**
Organization	Management Responsibility	Management requirements 4.1 Organization and management responsibility 4.2 Quality management system 4.15 Management Review
Personnel	Personnel	
Equipment		
Purchasing and Inventory	Purchasing Controls	4.6 External services and supplies
Process Control	Acceptance Activities Production and Process Controls	
Document and Records	Document Controls Records	4.3 Document control 4.13 Control of records
Information Management		
Occurrence Management	Nonconforming Product Corrective and Preventive Actions	4.8 Resolution of complaints 4.9 Identification and control of nonconformities 4.10 Corrective action

		4.11 Preventive action
Assessments	Quality Audit	4.14 Evaluation and audits
Process Improvement		4.12 Continual improvement
Facilities and Safety		
Service and Satisfaction	Servicing	4.4 Service agreements
	Handling, Storage, Distribution and Installation	
		4.7 Advisory services
		4.5 Examination by referral laboratories
	Design Controls	
	Labeling and Packaging controls	
	Identification and Traceability	

Note: The activities described in some of the 21 CFR 820 clauses have no corresponding clauses within other management standards and will require adjustment.

For a comprehensive description of all tasks and activities associated with each QSR see the 21 CFR 820 standard at 21 CFR 820 Standard. [41]

Implementation Step

This phase requires assigned personnel to perform a review and to document alignment of the management principles from the above standards to existing documents. This step requires the review of all applicable requirements, organizational guidance documents and accreditation general and technical checklists. The goal of this assessment is to develop a checklist of documents that are incomplete or missing. (Table.20) The following is required to perform this step:

1. Personnel familiar and well versed in laboratory terms and definitions
2. All applicable guidance documents
3. Checklist

Table 20: Example checklist

Checklist	Exists	Does Not Exist
12 QSE are implemented in the laboratory		
21 CFR 820 activities have been implemented		
Design Control: Identify all activities that do not exist in the laboratory		
Other regulations		

Direction: From the checklist, assign staff to develop the appropriate guidance documents in compliance with all requirements.

PRE-ASSESSMENT AND DOCUMENT CONTROL ACTION ITEMS: Confirm the following:

1. Document all activities implemented to adhere to standard

Example

Process	Alignment Confirmed			
	Policy	Procedure	Process	Training
1. Nonconforming Event	X	X	X	X

Phase IV: Design Control Translated to Operational Terms

Design Control comparable to a product development methodology, was originally established for the medical device industry and was intended to manage the process of "designing purchasing, manufacturing, packaging, labeling, storing, installing and servicing throughout the entire product lifecycle. [14] Design control applicable to the laboratory will require the development of organic processes translated into policies, processes, procedures that capture all aspects of test development with upstream and downstream links specific to each element of design control. The potential exists for the laboratory to have established processes that already adhere to one or more elements of design control. Design control applicable to the laboratory include documentation of changes, review and approval at each step as described in a Design History file. See 21 CFR 820 QSR for each element of design control. (Appendix C.) [14]

Table 21: Description of each element of design control with suggestions for procedures

Step	21 CFR 820 Design Control	Description
1	Design and Development Planning	Guidance regarding the plan, design, development, execution, involvement, interface with different groups and responsibility for LDTs.
2	Design Input	Procedure that describes 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 each step.
3	Design Output	Procedure that describes the output of the design, provides rationale, performance, specifications and criteria for verification that the design successfully transferred into the testing environment.
4	Design Review	Procedure that describes how all phases of the design will be reviewed with documentation and approval at each step. Laboratories are required to establish and maintain procedures for the identification, documentation, and validation, verification, review, and approval of design changes before implementation.
5	Design Verification	Procedure for determining that the test is safe, effective for use, conforms to the needs of the user and meets its intended use. Following the procedure ensures the design works as intended and has been verified, documented and approved at each activity level.

6	Design Validation	Procedure to assure that validation is performed under defined operating conditions to ensure the test is appropriate for the intended use.
7	Design Transfer	Procedure to describe the accurate transfer of the design into manufacturing requirements.
8	Design Changes	Procedure to identify, track, document and approve changes prior to each change event.
9	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.

Direction: Review each pertinent element of design control as depicted in Figure 21 and identify, develop and implement a guidance document for each topic.

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:

Design Control	Confirmed			
	Policy	Procedure	Process	Training
Design planning and development	X	X	X	X
Design input				
Design output				
Design review				
Design verification				
Design validation				
Design transfer				
Design changes				
Design history				
Design transfer				

Phase V: Process Controls

Clinical Validity

Clinical validity defined as the "accuracy with which a test can predict the presence or absence of the phenotype or clinical disease" [51] is currently limited to CLIA oversite for analytical validation of tests. In addition, the FDA has proposed enforcement for clinical validation of tests to include the establishment of the following: [50], [55]

1. Accuracy
2. Precision

3. Reportable ranges
4. Reference intervals
5. Interferences

For more information regarding Clinical Validity see CLIA regulations.

Directions: To ensure the clinical validity of a test protocol list the pertinent performance characteristics and reference ranges for LDT:

PROCESS CONTROL ACTION ITEMS: Performance Characteristics

Performance Characteristics	Reference Range

Phase VI: Process Validation plan

To validate the effectiveness of the framework and ensure all tasks and activities meet the regulation requirements, a validation protocol is developed to determine if the system is capable of managing test variation with fluctuating volume in an agile environment characteristic of LDT. A process validation protocol is utilized to ensure the LDT test development framework operates as intended. [37]

The validation plan includes: Process Qualification, (PQ) Operational Qualification (OQ), and Performance Qualification (PFQ) to verify all steps in the process meet or exceed regulatory requirements.

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 that the process is operating as intended.

Performance Qualification: (PFQ) demonstrates that the process consistently produces the same result and operates correctly when used at defined capacities. Activities included in the PFQ will test the entire system within the designed processes of the department, stress the system with a documented the response, and ensure that quality checks on tests have been performed. This PFQ stage of validation will test the overall process and ensure the system is performing as intended. Figure.14 lists all factors suggested for review at each stage:

The validation items are as follows:

Process Qualification (PQ)	*Operational Qualification (OQ)*	*Performance Qualification (PQ)*
Item	**Item**	**Item**
Research Design approval	Test protocol is complete	Quality control checks
Employees are trained	Patient/Clinician involvement	Reagent QC testing
Equipment maintenance	Guidance documents	Available supplies/reagents
Polices developed/revised	Supplier qualification/performance	Process owners
Supplies planned in advance	Quality control	Discrepancies are noted/resolved
Equipment validation	Standardized processes	Document control
Design control guidance	Design transfer	Employees are trained/competent
Origin of an LDT	Design changes	
Proof of Concept	Design history file	
Protocol: Design & Development	Design validation	
Input & output design	Equipment validation	
Quality control documentation	Gaps - regulatory requirements	
Equipment validation	Gaps in the process	
Training records	Supervisor oversight	
Testing equipment	Electronic tracking	
Materials / reagents		
Supplier Qualification		
Regulatory guidelines		

Figure 14: Factors that comprise a validation protocol

Directions: Develop and implement the following:

PROCESS VALIDATION ACTION ITEMS: Validation Protocol

Confirm implementation of the following	Completed:
Validation plan	
Validation protocol a. Process Qualification	
b. Operational Qualification	
c. Performance Qualification	
Validation Summary and Approval	

Phase VII. Adoption of an Agile Stage Gate Hybrid Technique for LDT development

The Agile Stage Gate Hybrid technique is a combination of two common product development methodologies that divide activities into stages separated by decision points. Each decision point is a go (approval)/no-go (rejection) of each stage. [47] Agile was initially developed to expedite software development; however, per Cooper, (2016) the combination of Agile with the Stage Gate method of product development has yielded favorable advantages to industries outside of software development and this technique has been shown to improve productivity and increase speed. [48]

The Agile Stage Gate Hybrid technique begins with strategic directives to plan and execute the project as it moves through design, development, testing, validation and launch. An owner is assigned to perform the tasks of go/no-go at each step and the process is further managed through the assignment of a cross-functional team to document details, to manage the process and to initiate a list of missing activities for each project that is rejected at the gate. The process may include

multiple iterations of projects at each stage. To confirm that no project is delayed, a daily follow up meeting is conducted to review current progress and to review prior commitments for each phase which remain incomplete (backlog). [48] A designated team lead is assigned to manage, perform and document a comprehensive review at each step and this information is discussed at these brief daily meetings. The meetings capture progress, challenges and areas of improvement which are then documented on white boards. By clearly communicating requirements, this approach to a launch will expedite the process and will allow for just-in-time response, resolution and documentation to meet rapidly changing needs. The goal of the meetings is to answer the following questions:[48]

1. From voice of the customer - what does the internal/external customer value?
2. What are the deliverables that will address these values within the next phase?
3. What tasks are needed achieve the desired outcome?

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

Applicable to LDT development, the process is reflective of design control beginning with test concept and ending with a post launch review. Each phase includes a daily review, discussion of the backlog, evaluation of user needs, a sprint (iteration) and back to the daily review as depicted in Figure 15.

The responsibilities include the following:

1. Leadership oversite and responsibility for the progress of the project and for removing barriers
2. Process owner to stop the process as needed

3. Knowledgeable cross functional team as subject matter experts with process responsibility and dedicated space to conduct daily meetings
4. Stage gate go/no-go position performs the following functions:
    a. Inspection/review/documentation at each step
    b. Design change/review/documentation
    c. Design history/review/documentation
    d. Design review/documentation

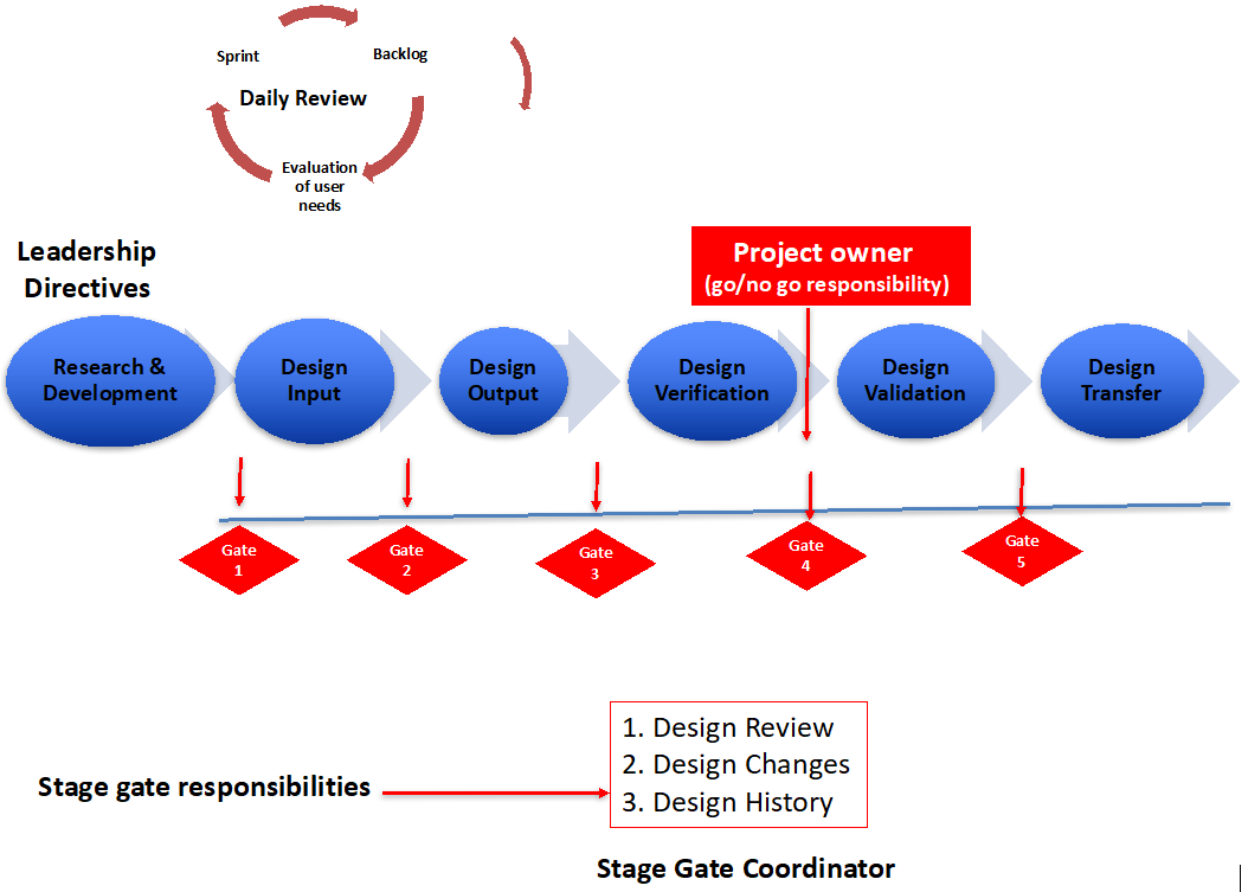


Figure 15: Agile Stage Gate Hybrid model for LDT development

Directions: Review and implement the list of items necessary for adoption of an Agile Stage Hybrid technique for LDT development.

Discussion

The LDT discussion began when we attempted to answer the question, "is compliance to the draft guidance possible, and if not, why not and what are the constraints?" [44] To answer this question, we conducted interviews with experts in the field of LDT. We proposed and tested factors translated from their responses and concluded the suggested factors were optimal for development of a regulatory QMS. Conversely, the understanding of regulatory requirements, translation of those requirements (design control) to operational processes and the assurance of performance through process validation were unclear. [44]

The lack of understanding by the laboratory community and the need for a regulatory QMS was further supported by Liz Lison, president of Advocea Consulting firm (2015) and a 2015 FDA Work Shop speaker that stated, "Most of the failures that I have seen in LDT may have been averted if design controls had been in place." [39]

To assist laboratories, consider the adoption of design control, we provide a support structure to define regulatory terms, recognize the current laboratory structure and implement missing elements in comparison to the QSR. Moreover, we suggest a systematic approach to implementation of design control through an agile stage gate technique for test development by leadership oversite, assignment of owner accountability, teams, sprints and noted responsibility. We illustrate a standardized, consistent pathway for LDT development by the delegation of a stage gate coordinator tasked to perform design control reviews, changes and documentation of history requirements at each stage gate.

This systematic approach to implementation of a regulatory QMS, will simplify the translation of medical device requirements to the diagnostic laboratory. Once considered impracticable and unachievable is now promising through the attainment of knowledge, creativity

and the enthusiasm for change. Mahatma Gandhi reminds us “we need not wait to see what others do” but, to be the change we want to see in the world. That will require moving past the status quo as seen in many laboratories today as *this is the way we have always done things* to how can we improve the process that will ultimately ensure patient safety?

CHAPTER 6: CONCLUSION & DIRECTIONS FOR FUTURE RESEARCH

Conclusion

The impetus for change within the laboratory environment began with the awareness of patients adversely affected by outcomes associated with Laboratory Developed Tests. Consequently, the design, development and manufacture of LDTs is not under the jurisdiction of CLIA and testing operations is not formally within the oversight of the FDA.

The interviews with nine expert senior professional leaders within in the field of LDT across regulatory, laboratory, accreditation and medical device industries served as the authority based on their stature and established the consensus for the response of topics discussed. Many interviewees claim the laboratories offer a "service, not a medical device" and furthermore, the FDA has no jurisdiction over LDT. [1] However, before proposed legislation can occur the agencies must bridge the gap between required regulations. Shelia Walcoff of Goldbug Strategies (2015) and a FDA Work Shop speaker stated that "It is essential that FDA harmonize the QSR requirements with CLIA requirements at a more granular level to prevent duplicate efforts and to ease the regulatory burden" because governmental agencies have not provided the necessary guidance for struggling laboratories." [39]

The interviewees shared this concern for CLIA and the FDA, however, before legislation can occur the agencies must collectively develop standards and guidance documents prior to a policy release because laboratories are misguided and unclear how FDA regulations translate to the laboratory. The adoption of a quality system regulation to ensure accurate test development appears incomprehensible under current laboratory operating structure. The lack of standards has resulted in fluctuating levels of quality within laboratories and implementation of process standardization and 12 Quality system essentials is based on the support of leaders to own and

drive an organic, directed initiatives with tasks and activities applied to local specific organizational processes. [53] A call for action has been initiated to promote proactive leadership commitment to prepare laboratories for the inevitable.

Moreover, the current FDA regulations 21 CFR 820 are developed for medical device and translation to operational laboratory terms does not exist. As a result, laboratories are taking the wait and see approach and have not registered their tests with the FDA, meanwhile, the FDA continues to understand the testing needs of the laboratories. The absence of test registration creates the inability of the regulatory agencies to create a standard reporting structure; without a standard reporting structure, laboratories continue to struggle to understand how these proposed changes will affect current operations. Gatter, (2017) has stated "it is unlikely that the issue is over ".[42] In fact, in the January 13, 2017 discussion paper the FDA indicates support for CLIA requirements regardless of the dissimilarity to 21 CFR 820 Quality System Regulation requirements and continues to recommend a QSR "consistent with the approach described in the discussion paper" for FDA requirements not mandated by CLIA. [6]

In support of the FDA Discussion paper, the survey respondents agreed that a regulatory oriented framework for the development of LDTs is needed in the laboratory. This was substantiated by results of exploratory research that included responses from 51 survey respondents out of a population of 767 attendees at the Executive War College Laboratory Conference in New Orleans, May 2016. Although the survey was sent to a large population of conference attendees the population included leaders within all areas of the laboratory including: sales, diagnostic imaging, medical device, diagnostic laboratories, reimbursement firms and many others. Moreover, the field of LDT is a small niche market so the response rate of 51 survey participants was a result of actual attendees that claimed to be experts in the field of LDT.

It was interesting to note that the survey respondents as experts in the field of LDT did not consider design control as extremely or very important despite the proposal for a QSR by the FDA. In addition, the eight suggested strategic factors and 40 statements derived from the literature, interviews and the FDA work shop provided the impetus for design of an QMS regulatory framework.

The respondents agreed with all statements relevant to the design of a QMS based on needs and gaps expressed by laboratory professionals. This finding aligns with the results of the survey as there was no significant difference in the way the experts verse non- experts responded to factors and associated statements. All respondents chose most statements as 1) extremely important or 2) very important. This finding aligns with the recommendation by Katherine Tynan, an independent regulatory consultant from the 2015 FDA workshop that offered advice to governmental agencies as follows:

4. "Develop a common vocabulary that laboratories can understand"
5. "Simplified the cumbersome QSR and assist laboratories translate the directives"
6. "Develop a "QSR fit for purpose and harmonize the standard"

Katherine's advice to laboratories was to "invest in a quality management system, implement all factors of design control, and be proactive and prepare for future regulatory requirements." [39] Consequently, the interviewees agreed that the terms, expectation and current recommendations lack user definition, specific methods for testing protocols, and clear testing requirements. The preparation of a QMS require the understanding where gaps exist to develop appropriate processes that would to adhere to requirements, however, the survey statement suggesting review of current policies and procedures to identify gaps was not considered important by all groups. This was an interesting conclusion, since this is general practice within laboratory accreditation agencies.

A process to incorporate the accreditation and regulatory standards has been customized from product development to test development for the diagnostic laboratory. The agile stage gate hybrid technique incorporates design control with the assignment of process owners, cross functional teams, and a stage gate coordinator to perform review, changes and history tasks and activities.

Resolution of Research Questions

The research question 1: Can laboratories operationalize a quality management framework that will meet FDA requirements? The preparation of a QMS necessitates laboratory leadership to understand the proposal by the FDA regarding all facets of LDT, take the initiative and provide the appropriate resources to bridge the gap from an accreditation focused operating structure to a regulatory framework. The survey participants concurred that the most favorable factors to design and implement a regulatory QMS consist of tasks and activities associated with the following categories: 1) Leadership, training, pre- assessment, 2) design control, 3) document control, 4) process control, 5) development of a QMS framework and 6) process validation. The test development process is then navigated through the agile stage gate hybrid technique to expedite test development to satisfy the supply chain of service, process and people.

Research question number 2: Will an adoption of a quality system framework provide the manufacturing foundation that will adhere to 21 CFR 820 Design Controls?

The manufacturing foundation built from the strategic factors discussed above is expanded to include tasks and activities within each element of design control. This customized product development methodology translated from medical device to the laboratory testing environment is further expanded by utilization of the agile stage gate hybrid technique for LDT launch. The technique is customized by the establishment of laboratory leads as owners that contain the

authority to reject and stop the process due to quality concerns. In addition, the role of stage gate coordinator was established as an objective position to perform review at each gate and document changes and history throughout test development.

Directions for Future Research

The future research in the field of LDT can be pursued along four areas: 1) Live pilots for the development of a regulatory QMS for in-house LDTs, 2) Product development methodology adaptable to the laboratory, 3) Implication of venture capitalist funding/support for or against LDT development, and 4) Enhancement of current regulations for the adoption, clarification and registration of tests for risk assessment.

1) I plan to be involved with a pilot to be conducted in a live environment at the Department of Defense in Washington DC. The goal of this pilot is to demonstrate and substantiate outcome measures, lessons learned and the feasibility to move laboratories from the status quo to a system designed for patient safety. This approach will require proactive leadership, resources, creativity and innovation and may be considered the most significant step towards diffusion since development of the Laboratory Improvement Amendment Act (CLIA) under the Centers for Medicare and Medicaid Services (CMS) in 1967, 1988. [4] The live pilot in the laboratory will investigate the need for "tailored" framework developed for the LDT community based on test complexity, risk, and volume.

2) Another area for future research is the adoption of a product development methodology to the laboratory environment to address risk management, test allocation, planning and implications of limited resources across a portfolio management approach to LDT development with the opportunity to explore share resources and components for similar tests access multiple laboratories.

3) Another line of extension for future research would be to investigate the influence of venture capital (VC) funding for LDT development. While VC funds would be interested in quicker and larger returns on investment (ROI), they would also be concerned about adverse health risk events associated with the tests. It would be interesting to investigate whether this would require any modifications to the proposed QMS framework.

4) Establishment of technical requirements associated with clinical validity, performance characteristics or risk classification addressed in more detail by the CLIA under the Centers or Medicare and Medicaid.

APPENDIX A. E-MAIL INVITE FOR INTERVIEW

Good afternoon,

My name is Rita D'Angelo, the former Quality Manager from Henry Ford Health System, Pathology and Laboratory Medicine in Detroit, Michigan.

I am currently working on my Ph.D. dissertation and I'm seeking an understanding and clarification on the regulatory perspective of Laboratory Developed Tests.

Are you available for a 30-minute phone interview to answer a few questions regarding the position of CAP accreditation/CLIA, FDA and the future implication for laboratories?

Thank you for your assistance and participation.

Warm regards,

Rita D'Angelo

PHD Candidate

Wayne State University

APPENDIX B. INTERVIEW PROTOCOL- LABORATORY DEVELOPED TESTS

Date: _____

Interviewer initials:	Time frame of Interview:
Interviewee initials:	Location:
Event #	Recording #

Introduction

Hello, my name is Rita D'Angelo and I am a student of Wayne State University working towards my Ph.D. dissertation. I am conducting research to learn about the process of Laboratory Developed Testing (LDT protocols within medical laboratories. I would like to understand more about this topic from the perspective of governmental policy, challenges of Laboratory leadership and potential process changes. I sincerely appreciate your assistance and making the time available for me to ask you some questions.

The goal of this interview is to learn your perspective, understanding and outlook on Laboratory Developed Tests as it relates to the overarching federal requirements and future strategy. I encourage you to be as open and candid with me as possible and I pledge to keep your responses confidential. I will interview many staff members that have a direct responsibility, oversight or outcome associated with Laboratory Developed Tests. I am searching for strategy, future direction and process related information across the interviews. I will compile findings and summarize the results without identifying anyone specifically.

Do I have your permission to record this interview? This will allow me to time to document and verify the accuracy of my notes. Recordings will not be shared with anyone and will be destroyed

at the conclusion of our project. Please feel free at any time to ask me to stop the recorder if you want to say something or alert me if you do not wish to be recorded. Can I proceed?

Feel free to ask any questions before we begin.

1. What is your role and responsibility in the organization?
    a. What is your title?
2. Tell me about the history and your knowledge about of Lab developed Tests?
3. What are some of the regulatory challenges associated with LDT's?
4. How does genetic testing influence regulatory oversight?
5. Describe the current scrutiny associated with regulatory guidelines for LDT's?
6. What is the role of the FDA in lab developed tests?
7. Explain the intent of the FDA guidance framework for LDT's released December 2014?
8. In your opinion, what would the implications(s) be if the FDA mandated regulatory guidelines for the process of LDT's?
9. How would you describe the "outcome and view of the future" if the FDA mandates regulatory oversight for LDT's?

Thank you for your time and attention. This is the conclusion of the interview. Please do not share these questions with anyone.

If you think of anything else that you would like to share or if you know someone else that would be beneficial in this process, feel free to contact me by e-mail or phone. All interactions, information and conversations are maintained as confidential.

Thank you!

Follow-up-Name:	Date of Follow-up;

Next meeting-Name:	Date of Next Meeting:

APPENDIX C. DESIGN CONTROL

General. (1) Each manufacturer of any class III or class II device, and the class I devices listed in paragraph (a)(2) of this section, shall establish and maintain procedures to control the design of the device in order to ensure that specified design requirements are met.

(b) *Design and development planning.* Each manufacturer shall establish and maintain plans that describe or reference the design and development activities and define responsibility for implementation. The plans shall identify and describe the interfaces with different groups or activities that provide, or result in, input to the design and development process. The plans shall be reviewed, updated, and approved as design and development evolves.

(c) *Design input.* Each manufacturer shall establish and maintain procedures to ensure that the design requirements relating to a device are appropriate and address the intended use of the device, including the needs of the user and patient. The procedures shall include a mechanism for addressing incomplete, ambiguous, or conflicting requirements. The design input requirements shall be documented and shall be reviewed and approved by a designated individual(s). The approval, including the date and signature of the individual(s) approving the requirements, shall be documented.

(d) *Design output.* Each manufacturer shall establish and maintain procedures for defining and documenting design output in terms that allow an adequate evaluation of conformance to design input requirements. Design output procedures shall contain or make reference to acceptance criteria and shall ensure that those design outputs that are essential for the proper functioning of the device are identified. Design output shall be documented, reviewed, and approved before release. The approval, including the date and signature of the individual(s) approving the output, shall be documented.

(e) *Design review.* Each manufacturer shall establish and maintain procedures to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development. The procedures shall ensure that participants at each design review include representatives of all functions concerned with the design stage being reviewed and an individual(s) who does not have direct responsibility for the design stage being reviewed, as well as any specialists needed. The results of a design review, including identification of the design, the date, and the individual(s) performing the review, shall be documented in the design history file (the DHF). (f) *Design verification.* Each manufacturer shall establish and maintain procedures for verifying the device design. Design verification shall confirm that the design output meets the design input requirements. The results of the design verification, including identification of the design, method(s), the date, and the individual(s) performing the verification, shall be documented in the DHF.

(g) *Design validation.* Each manufacturer shall establish and maintain procedures for validating the device design. Design validation shall be performed under defined operating conditions on initial production units, lots, or batches, or their equivalents. Design validation shall ensure that devices conform to defined user needs and intended uses and shall include testing of production units under actual or simulated use conditions. Design validation shall include software validation and risk analysis, where appropriate. The results of the design validation, including identification of the design, method(s), the date, and the individual(s) performing the validation, shall be documented in the DHF.

(h) *Design transfer.* Each manufacturer shall establish and maintain procedures to ensure that the device design is correctly translated into production specifications.

(i) *Design changes.* Each manufacturer shall establish and maintain procedures for the identification, documentation, and validation or where appropriate verification, review, and approval of design changes before their implementation. (j) *Design history file.* Each manufacturer shall establish and maintain a DHF for each type of device. The DHF shall contain or reference the records necessary to demonstrate that the design was developed in accordance with the approved design plan and the requirements of this part.

Source: 21 CFR 820, Design Controls, FDA (2014)

APPENDIX D. LABORATORY ASSESSEMENT WORKSHEET

Assessment Statement

	Exists	**Does Not Exist**
1. All 12 QSE are implemented in the laboratory		
2. List missing QSE		
3. QSE comply with QSR		
4. Identify all outliers		
5. All 21 CFR 820 activities have been implemented		
6. Design Control: Identify all activities that do not exist in the laboratory		
7. All elements of design control have been implemented		
8. There is documentation for research and development of test design and service development.		
9. Responsibility for design and development activities are defined		
10. Design input, review and output activities are defined.		
11. Documentation exists for design and history of change.		
12. There is documentation for design transfer to testing parameters		
13. Documentation exists for initiation of LDT		
14. Logistics are in place to support the supply chain		

15. A process in place to secure appropriate supplies and reagents

16. There are procedures and processes for supplier qualification

17. There a process for supplier performance and monitoring

18. Design control elements are applied

19. There is validation plans for equipment and processes

20. Customer supplier interaction exists throughout the lifecycle to resolve discrepancies and documentation maintained

21. Quality control performed for all testing and records are maintained

22. A standard format exists for result reporting

23. Policies, procedures or processes

APPENDIX E. QUALTRICS SURVEY RESULTS: MANAGEMENT CATEGORIES AND 40 STATEMENTS

Q1: Leadership

Statement 1: Leadership institutes key performance indicators that outline, measure and direct regulatory initiatives

Statement 2: Leadership commitment to initiate and maintain change in the organization

Statement 3: The establishment of a QMS includes oversight by a knowledgeable, educated, responsible, informed, cohesive team to effectively manage the process

Statement 4: Establishment of an LDT quality committee to quickly approve changes and provide support

Statement 5: Leadership consistently communicates change

Q2: Training

Statement 6: The training program includes a basic introduction to the manufacture of LDTs and the roles and responsibility of leaders and staff

Statement 7: The course material includes regulatory requirements and terms and definitions in alignment with CLIA 88, 12 QSEs, 21 CFR 820/Q SR and Design Control

Statement 8: The program includes value stream mapping to demonstrate the significance of hand- offs, tasks and activities and all aspects of the LDT process beginning with research and development and ending with diagnostic testing

Statement 9: Staff training includes the process of successfully navigating the LDTs through the system to ensure all changes are well reviewed, documented and communicated

Statement 10: The assignment of responsible persons(s) to address, resolve, communicate and document testing concerns

Q3: Pre- assessment

Statement 11: The review of existing laboratory processes in comparison to the list of 12 QSE management principles will identify policies, procedures or processes not previously addressed

Statement 12: Quality management standards, such as ISO 15189 if executed to completion will better prepare the organization to comply with regulatory requirements

Statement 13: A cross walk of current processes in comparison to 21 CFR 820 quality system regulation will assist laboratory leaders identify and understand pertinent gaps in the QMS

Statement 14: A pre- assessment of existing policies, procedures and processes may reveal informal processes or documents not previously considered compliance to a regulatory requirement

Statement 15: A clear understanding the QSR requirements is key to implementing processes for a robust quality management system

Q4: Design Control

Statement 16: Implementation of all aspects of design control including design, development, input, output, review, verification, transfer, changes and history will demonstrate adherence to regulatory requirements and patient safety

Statement 17: Design control described in laboratory terms will clarify the requirements for translation and adaptability to the laboratory environment

Statement 18: Design control well implemented and documented will ensure quality is built into every step

Statement 19: The translation of 21 CFR 820 requirements into laboratory terms will highlight and address the content required for the development of standard operating procedures

Statement 20: A procedure that address the process for identification, documentation and reporting of an adverse event is referred to as medical device reporting

Q5: Document Control

Statement 21: Updated and accurate standard operating procedures serves as verification of compliance

Statement 22: A clearly written procedure for each phase of test development will remove any ambiguity in the process

Statement 23: Record retention and timely retrieval of documentation related to the design, manufacture and testing of LDTs demonstrated regulatory compliance

Statement 24: Documentation of tasks and activities at each step of the test development process is captured, reviewed and approved to address the design history requirement

Statement 25: A document control system will ensure documents are current and are readily available

Q6: Process Control

Statement 26: The process of LDT manufacture include assigned tasks and responsibility at every hand- off to ensure concerns are identified, resolved, documented and communicated

Statement 27: The consistent uninterrupted flow of material, product, and information between handoffs is critical to demonstrate the user friendliness of the framework

Statement 28: Documentation of analytical validity will demonstrate and document the accuracy and reliability of test performance

Statement 29: Clinical validity is performed to validate whether the design and optimization of the test protocol will yield testing outcomes that can be used to develop a useful clinical intervention

Statement 30: Data collection and clearly communicating requirements in an LDT launch will expedite the process and will allow for just-in-time response and resolution to meet rapidly changing needs

Q7: Development of a QMS Framework

Statement 31: The primary step to develop a regulatory QMS is to define a leadership support structure with defined roles, responsibilities and oversight

Statement 32: Employee training describes terms definitions and regulatory requirements for the development, manufacture and testing of LDTs

Statement 33: Performance of a cross walk or pre- assessment to detect all aspects of the current QMS in comparison to CLSI and QSR requirements

Statement 34: Review the pre- assessment findings and create a list of necessary guidance documents in need of development

Statement 35: Develop missing policies, procedures and processes to comply with regulatory requirements

Q8: Process Validation

Statement 36: Process validation is performed to ensure effectiveness of the framework

Statement 37: A validation plan includes Process Qualification(PQ), Operational Qualification(OP) and Performance Qualification(PFQ) to verify that all steps in the process meet or exceed regulatory requirements

Statement 38: Process Qualification (PQ) ensures the necessary components of the process are implemented according to design specifications. Documents necessary for operation, performance and maintenance are verified and the process includes all pertinent factors.

Statement 39: Operational Qualification will ensure the process is operating as intended

Statement 40: Performance qualification (PFQ) demonstrates the process consistently produces the same result and operates correctly when used at defines capacities.

APPENDIX F. INTERVIEW RESULTS

Interview Topic # 1: Risk Classification

The most critical ambiguity mentioned ten times within all nine interviewees was the inability to identify testing categories into high, moderate or low classifications and the process of LDT registration. There is no current LDT approval process in place and very "few laboratories have registered their LDT with the FDA." (Interviewee # 7) Because very few laboratories have taken this proactive step no "precedent has been set" (Interviewee # 7) making the test approval process daunting at best. Despite the lack of clarity by the FDA, New York State (NYS) has currently mandated all laboratories that develop LDTs to register their tests and classify their risk as of November 14, 2016.[3]

Interview Topic # 2: Validation of Test Systems

Another common theme among the participants was the accuracy of test development and validation to ensure patient safety. Interviewees emphasized the importance of systems to validate protocols, processes and test development that will consistently ensure the effectiveness and accuracy of test results. All interviewees shared a common concern regarding the effectiveness of test validation and future requirements to formally "test an ample number of samples to substantiate the intended outcome" (Interviewee # 3).

Interview Topic # 3: Uncertainty Over Future LDT Mandates

There was significant trepidation expressed by all interviewees regarding the uncertain future of FDA mandates over every aspect of the LDT process. The participants expressed concern and ambiguity regarding the draft guidance and its consequences should it become final policy. For example, if the FDA mandates clinical trials for the development of high-risk tests, as required for medical devices, many smaller laboratories without adequate resources may find it necessary to

outsource their LDTs, discontinue them, or partner with larger laboratories. This concern is substantiated by Klein,(2016) who states that significant financial consequences exist for laboratories and that the proposal as written could cause discontinuance of many LDTs.[12] Larger laboratories, including reference laboratories, have a competitive edge over smaller labs, including the utilization of advanced genetic testing technology like Next Generation sequencing. This technology generates enormous amounts of disease-related data in real time, and in support of LDT development and validation.

Interview Topic #4: Patient Safety Measures of Accuracy and Efficacy

Eight participants expressed concerns that the lack of regulatory oversight for LDTs may have led to adverse patient safety outcomes such as the misdiagnosis of serious illness as a result of inaccuracies of testing protocols and their results. Additionally, patients may have been treated for disease they did not have, or did not receive treatment for diseases they did have. The common sentiment expressed during these interviews was of the need for thoughtful consideration of the accuracy of test development, safe-testing practices, test verification and reproducibility of results. The interviewees described their concern for accurate testing outcomes and process validation. One participant stated that process validation "is critical to ensure the safety of the patient and should be considered the standard of care" (Interviewee # 2).

Interview Topic # 5: Adopting a Quality System Regulation Framework

Six participants discussed their concern for laboratories being able to adopt this framework and raise the level of quality within their organizations. They shared a common response that laboratories lacked the rigor that is required for the manufacture of medical devices, and that could translate to LDT development. Change is necessary in order to raise the level of quality, prioritize tasks and dedicate the time and resources necessary to understand regulatory requirements in order

to attain process standardization. Ambiguity existed during the interviews regarding the definition of design control and how to appropriately address these requirements. As reinforcement of this, Liz Lison, president of Advocea Consulting firm and a conference speaker at the 2015 FDA Workshop on Laboratory Developed Tests explained, "Most of the failures that I have seen in LDTs may have been averted if design controls had been in place. Therefore, I urge the agency not to delay the enforcement of design controls for high-risk tests and potentially introduce a two -tier system for pre-market review".[13]

Interview Topic # 6: Accreditation

Six participants stated that the FDA lacks the resources necessary to inspect all labs across the USA and would eventually require the assistance from third party accreditation agencies. As stated in their 2017 Discussion Paper, the FDA explains, "expansion of inspection will include a "third party inspection program for LDTs so that many of these post-market inspections could be conducted by FDA-accredited third parties. This would allow such third parties, when appropriate, to inspect for the three additional FDA QS requirements at the time of a routine CLIA survey inspection."[14] The FDA appears to be working towards this by exploring opportunities to coordinate with and leverage existing programs such New York and other programs managed by organizations approved by CLIA.[14]

Interview Topic #7: Quality Management System

Four interviewees indicated that in the absence of a policy and a defined set of standards, laboratories will likely take the wait and see approach, not progressing with change or development until required. Because "development of a quality structure takes a considerable amount of time" (Interviewee #3), laboratories should consider whether to prepare in anticipation of regulatory changes. In the face of uncertainty over how 21 CFR 820 requirements applies to laboratory testing

services, laboratory leaders need greater clarity on understanding and preparing for a QSR framework. Katherine Tynan, an independent regulatory consultant at the 2015 FDA Work shop on Laboratory Developed Tests, expressed her concerns and offered advice to governmental agencies as follows: [13]

- "Develop a common vocabulary that laboratories can understand"
- "Simplified the cumbersome QSR and assist laboratories translate the directives"
- "Develop a "QSR fit for purpose and harmonize the standard"

Her advice to laboratories was to "invest in a quality management system, implement all factors of design control, and be proactive and prepare for future regulatory requirements."[13] However, laboratories lack guidance and direction and the current historical documents refer to medical device, rather than laboratories. Translation of the requirements to practical laboratory language is not easy, and the resources required for development of a structure to comply with regulatory requirements is difficult to estimate.

The Clinical Laboratory Improvement Act has not updated the original laboratory standard since 1988. Four interviewees expressed the need for CMS and the FDA to reach an understanding regarding requirements and aim towards consistency of purpose prior to a policy release. Shelia Walcoff of Goldbug Strategies at the 2015 FDA Work shop on Laboratory Developed Tests stated, "It is essential that FDA harmonize the QSR requirements with CLIA requirements at a more granular level to prevent duplicate efforts and to ease the regulatory burden, because governmental agencies have not provided the necessary guidance for struggling laboratories." [13] The FDA 2017 Discussion Paper addresses this concern by the following statement "Adapting CLIA to enable CMS to provide the kind of effective oversight of LDTs that is needed to ensure that they are accurate, reliable, and clinically valid would require a significant change in the nature of what the

agency does, rather than minor modifications as some have suggested. By its very nature, a CMS-only framework for LDTs could create costly federal redundancies and inefficiencies." [13] The oversight of laboratory testing remains with CMS (and CLIA), however, a gap exists regarding the regulation of test development. Due to the advances in genomic medicine the oversight by CLIA is no longer adequate to manage the compliance needs of laboratories. This is highlighted by the significant difference in the oversight between FDA and CLIA. The FDA does not mandate the operations of testing as stated in 21 CFR 820, while CLIA does not ensure the safety and effectiveness of test protocols as described in CFR 493. As stated by Interviewee # 1, "there are no plans for CLIA to update policies at this time."

APPENDIX G: SURVEY RESULTS: TOP TEN RESPONSES BY EXPERTS PER SIGNIFICANCE OF MEANS

1. **Leadership: Statement 1:** Leadership institutes key performance indicators that outline, measure and direct regulatory initiatives
2. **Leadership: Statement 2:** Leadership commitment to initiate and maintain change in the organization
3. **Leadership- Statement 3:** The establishment of a QMS includes oversight by a knowledgeable, educated, responsible, informed, cohesive team to effectively manage the process
4. **Leadership: Statement 5:** Leadership consistently communicates change
5. **Process Control: Statement 29:** Clinical validity is performed to validate whether the design and optimization of the test protocol will yield testing outcomes that can be used to develop a useful clinical intervention.
6. **Process Validation: Statement 37:** A validation plan includes: Process Qualification, (PQ) Operational Qualification (OQ), and Performance Qualification (PFQ) to verify that all steps in the process meet or exceed regulatory requirements
7. **Process validation: Statement 38:** Process Qualification: (PQ) ensures the necessary components of the process are implemented according to design specifications. Documents necessary for operation, performance and maintenance are verified and the process includes all pertinent factors
8. **Development of a QMS Framework: Statement 31-** The primary step to develop a regulatory QMS is to define a leadership support structure with defined roles, responsibilities, and oversight

9. **Training- Statement 7:** The course material includes regulatory requirements and terms and definitions in alignment with CLIA 88, 12 QSEs, 21 CFR 820/QSR and Design Control
10. **Document Control -Statement 25:** A document control system will ensure documents are current and are readily available

The MOST important responses by ALL groups per significance of means

1. **Leadership: Statement 2:** Leadership commitment to initiate and maintain change in the organization
2. **Leadership Statement 5:** Leadership consistently communicates change
3. **Leadership Statement 1:** Leadership institutes key performance indicators that outline, measure a**nd direct regulatory initiatives**
4. **Leadership Statement 3:** The establishment of a QMS includes oversight by a knowledgeable, educated, responsible, informed, cohesive team to effectively manage the process
5. **Process Control: Statement 29:** Clinical validity is performed to validate whether the design and optimization of the test protocol will yield testing outcomes that can be used to develop a useful clinical intervention
6. **Pre-Assessment of Existing QMS:** Statement 15: A clear understanding of the QSR requirements is key to implementing processes for a robust regulatory quality management system
7. **Process Validation Statement 37:** A validation plan includes: Process Qualification, (PQ) Operational Qualification (OQ), and Performance Qualification (PFQ) to verify that all steps in the process meet or exceed regulatory requirements

8. **Document Control Statement 25:** A document control system will ensure documents are current and are readily available
9. **Process Control Statement 28**: Documentation of analytical validity will demonstrate and document the accuracy and reliability of test performance

LEAST important responses by ALL groups per significance of means

1. **Development of a QMS Framework: Statement 32**: Employee training describes terms, definitions and regulatory requirements for the development, manufacture and testing of LDTs
2. **Development of a QMS Framework: Statement 34:** Review the pre- assessment findings and create a list of necessary guidance documents in need of development in comparison to 21 CFR 820 Quality System Regulation will assist laboratory leaders identify and understand pertinent gaps in the QMS
3. Pre-assessment of Existing Quality Management System
    a. **Statement 14:** A pre- assessment of existing policies, procedures and processes may reveal informal processes or documents not previously considered compliance to regulatory requirements
    b. **Statement 11:** The review of existing laboratory processes in comparison to the list of CLSI 12 QSE management principles will identify policies, procedures or processes not previously addressed
    c. **Statement 13:** A cross walk of current processes in comparison to 21 CFR 820 Quality System Regulation will assist laboratory leaders identify and understand pertinent gaps in the QMS

4. **Document Control: Statement 21:** Updated and accurate standard operating procedures serves as verification of compliance
5. **Training: Statement 8:** The program includes value stream mapping to demonstrate the significance of hand-offs, tasks and activities and all aspects of the LDT process beginning with research and development and ending with diagnostic testing
6. **Document Control: Statement 23:** Record retention and timely retrieval of documentation related to design manufacture and testing of LDTs demonstrate regulatory compliance
7. **Process Control: Statement 27:** The consistent uninterrupted flow of material, product, and information between hand- off s is critical to demonstrate the user- friendliness of the framework
8. **Leadership: Statement 4:** Establishment of an LDT quality committee to quickly approval changes and provide support
9. **Design Control: Statement 20:** A procedure that addresses the process for identification, documentation and reporting of an adverse event is referred to as Medical Device Reporting

LEAST important statements common to both groups

1. **Development of a QMS Framework: Statement 34:** Review the pre- assessment findings and create a list of necessary guidance documents in need of development
2. **Process Control: Statement 27:** The consistent uninterrupted flow of material, product, and information between hand- off s is critical to demonstrate the user- friendliness of the framework

3. **Pre-assessment of Existing QMS: Statement 13:** A cross walk of current processes in comparison to 21 CFR 820 Quality System Regulation will assist laboratory leaders identify and understand pertinent gaps in the QMS
4. **Pre-assessment of Existing QMS: Statement 14:** A pre- assessment of existing policies, procedures and processes may reveal informal processes or documents not previously considered compliance to regulatory requirement
5. **Leadership: Statement 4:** Establishment of an LDT quality committee to quickly approval changes and provide support
6. **Document Control: Statement 23:** Record retention and timely retrieval of documentation related to design, manufacture and testing of LDTs demonstrate regulatory compliance
7. **Training: Statement 8:** The program includes value stream mapping to demonstrate the significance of hand-offs, tasks and activities and all aspects of the LDT process beginning with research and development and ending with diagnostic testing
8. **Design Control: Statement 20:** A procedure that addresses the process for identification, documentation and reporting of an adverse event is referred to as Medical Device Reporting

Strategic Factors - Respondent Feedback

Q9, do you agree with the strategic factors identified in the proposed framework for Quality Management System of LDTs? If not, please suggest additional factors pertinent to develop a robust framework

1. Agree, and in fact these are important
2. I think all 12 QSES need to be applied to ANY laboratory project - particularly LDTs.

3. Aside from the strategic factors outlined I think it would important to get buy-in from leadership to allow for the time necessary for the implementation of these factors outside of normal work duties. In addition, each lab using these processes should have at least one go-to super user that can help navigate these processes.
4. An additional factor is a defined process for management to review and re-evaluate whether current resources (both personnel and equipment) are sufficient to address QMS gaps, maintain established processes, and implement changes

Feedback- The Establishment of a Quality Management System Framework

Q10 - Do you think the establishment of a Quality Management System framework will assist LDT laboratories incorporate regulatory requirements such as design control more readily? If not, why and what else is necessary?

1. A fully functional QMS is needed for a laboratory to meet accreditation requirements. Design and document control is paramount in having this happen.
2. The QMS framework will not only assist LDT Lab and also assist clinical lab as well in compliance with regulatory requirements
3. definitely yes and having a framework that is accepted throughout our industry will set a level playing 8eld as well provide structure, uniformity and integrity to the entire process
4. Yes, it could help by providing guidance. The biggest issue with some of the most complex LDT's is the clinical significance, and how results derived from a LDT are being used or will be used to guide therapy.
5. Yes, the QMS framework will provide these laboratories with the tools to ensure LDT development is conducted and documented consistently, with demonstration of regulatory compliance as a by-product.

6. Yes, a QMS is foundational to building LDTs into a lab.
7. I do think that you could crosswalk each clause of Part 820 to the elements of each QSE and use the QSEs as the QMS framework for LDTs. QSE Process Management would be the location of all Part 820 clauses related to design. Everything else in Part 820 comes from ISO 9001:1994 and sorts easily to each QSE. We used ISO 9011:1994 when we created the QSEs in 1998.

APPENDIX H: DESCRIPTIVE STATEMENTS

Descriptive statistics for all 40 statements with corresponding mean and standard deviation.

Descriptive Statistics					
	N	Minimum	Maximum	Mean	Std. Deviation
Q1_2	33	1	2	1.30	0.467
Q1_5	33	1	2	1.30	0.467
Q1_1	33	1	2	1.33	0.479
Q1_3	33	1	2	1.48	0.508
Q6_4	32	1	3	1.53	0.567
Q3_5	33	1	3	1.64	0.603
Q8_2	33	1	3	1.64	0.603
Q5_5	32	1	3	1.66	0.602
Q6_3	32	1	3	1.66	0.602
Q2_5	33	1	3	1.67	0.595
Q8_1	33	1	3	1.67	0.645
Q4_1	33	1	4	1.67	0.692
Q8_3	33	1	3	1.70	0.585
Q2_2	33	1	3	1.70	0.637
Q7_5	31	1	3	1.71	0.643
Q7_1	32	1	3	1.72	0.581
Q8_5	33	1	3	1.79	0.650
Q2_4	33	1	3	1.82	0.635
Q5_2	33	1	3	1.82	0.808

Q4_3	33	1	5	1.82	0.846
Q8_4	33	1	4	1.82	0.683
Q3_2	33	1	5	1.88	0.992
Q4_2	33	1	4	1.88	0.781
Q6_1	31	1	3	1.90	0.651
Q5_4	33	1	3	1.91	0.723
Q6_5	32	1	3	1.97	0.782
Q7_3	32	1	4	1.97	0.740
Q2_1	33	1	3	1.97	0.728
Q4_4	33	1	3	1.97	0.684
Q7_2	32	1	3	2.00	0.568
Q5_1	33	1	5	2.00	1.000
Q2_3	33	1	3	2.03	0.728
Q3_1	33	1	3	2.03	0.770
Q7_4	32	1	3	2.03	0.595
Q3_3	33	1	5	2.06	0.827
Q5_3	33	1	3	2.12	0.820
Q3_4	33	1	4	2.15	0.870
Q6_2	32	1	3	2.16	0.628
Q1_4	33	1	5	2.24	0.969
Q4_5	33	1	4	2.39	1.029
Valid N (list wise)	29				

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ABSTRACT

AN AGILE QUALITY MANAGEMENT SYSTEM FOR LABORATORY DEVELOPED TESTS

by

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Advisor: Dr. Ratna Babu Chinnam

Major: Industrial Engineering

Degree: Doctor of Philosophy

Statement of the Problem: We explore the 2014 draft guidance by the FDA entitled *Framework for Regulatory Oversight of Laboratory Developed Tests* (LDT) extended from the medical device industry and discuss how these requirements may be applicable to laboratory medicine. We introduce terms, definitions and provide a call for action for leaders to prepare for the potential adherence to regulatory requirements and explore if compliance was achievable in a laboratory environment to design, develop and validate Laboratory Developed Tests. If not, why not, and what would be the limiting steps.

Method: We perform interviews with laboratory professionals to explore their concerns and challenges regarding the FDA draft guidance then translate the results into strategic factors. Based on the feedback, we surveyed laboratory experts in the field of LDT to develop and test strategic factors that would comprise an effective quality management system framework (QMS) to comply with the FDA proposal. We describe the methodology to translate the strategic factors into a design that would transform the existing laboratory structure into a regulatory quality management system.

Conclusion: Nine interviewees and 35 survey respondents shared the importance of risk classification, process validation, patient safety and general ambiguity for the development of LDT. We utilize the top supporting statements and associated factors chosen by experts as extremely important for LDT development as the building blocks for implementation of a regulatory QMS framework. The framework includes six phases of implementation: 1) establishment of a leadership support structure, 2) training, 3) pre-assessment of current laboratory processes, 4) adoption of design control, 5) process controls, 6) process validation and the application of an agile Stage Gate technique for test development.

Respondents agree that a regulatory agile quality management system is needed in laboratories that develop LDT. Utilizing the strategic factors, we develop a novel approach to LDT design, development and testing that extends the existing laboratory structure with a proven product development methodology technique called agile stage gate hybrid with the assignment of dedicated, accountable cross-functional teams for go/no-go approvals at every step and institute a coordinator position to review, document and expedite LDT development throughout the testing process.

AUTOBIOGRAPHICAL STATEMENT

Rita D'Angelo is pursuing her Ph.D. full-time at Wayne State University and is an independent contractor that works to bring advantage to healthcare institutions in need through D'Angelo Advantage Consulting, LLC. D'Angelo has co-developed the Henry Ford Production System culture of continuous improvement based on principles of Toyota at Henry Ford Health System, Detroit, MI, and continues to assist laboratories implement Lean management. Rita has taught extensively in Lean over the past ten years and serves as faculty at Villanova University in the School of Professional Studies teaching Lean Six Sigma Black Belt for Healthcare.

Rita has led the multi-year initiative that culminated in the first ISO 15189 accreditation of an integrated system of laboratories in the United States and continues to assist diagnostic laboratories develop quality management systems in preparation for ISO 15189 international accreditation for medical competency. D'Angelo has a regulatory background with quality managerial experience at the American Red Cross, at an FDA-regulated chemical manufacturer, and as a laboratory inspector for the College of American Pathologists. She holds a Master of Health Administration degree, a Six Sigma Black Belt, Quality Engineer and Lean certifications.