THE APPLICATION OF LEAN THINKING TO PHARMACEUTICAL QUALITY SYSTEMS, DEFINING THE FDA AS THE CUSTOMER

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THESIS: THE APPLICATION OF LEAN THINKING TO PHARMACEUTICAL QUALITY SYSTEMS, DEFINING THE FDA AS THE CUSTOMER

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ABSTRACT

This thesis presents the theory of Lean Thinking and applies the processes and techniques identified for manufacturing operations to pharmaceutical quality systems under the Food and Drug Administration (FDA) regulation. The FDA is defined as the customer. The product is defined as the deliverables required by the FDA of the quality systems to ensure compliance with the applicable laws, regulations, and guidance documents.

The evolution of the FDA is examined to understand its intent in protecting the drug consumer, increasing authority, increasing enforcement capabilities, current expectations of pharmaceutical manufacturers, and the cost of non-compliance. The evolution of Lean Thinking is also examined. The five key principles of Lean Thinking: value definition, value stream identification, flow, pull, and perfection are extrapolated to pharmaceutical quality systems. This extrapolation results in a detailed identification of the quality systems components, their associated responsibilities, and the value streams necessary to ensure compliance.

CHAPTER 1

INTRODUCTION

Background

The background includes the evolution of the United States Food and Drug Administration (FDA) from its inception to its current, and increasing, level of regulation, enforcement authority, and quality requirements. This includes key laws and acts passed to provide protection to consumers of pharmaceutical products. A review of consumer injuries and deaths resulting from consumption of adulterated, unregulated, untested, and unapproved products that provide the driving force behind the regulations and acts follow. Enforcement activities by the FDA resulting from noncompliance are also reviewed. Finally, the evolution of lean thinking and the key benefits are reviewed.

From the beginning of civilization people have been concerned with the quality and safety of foods and medicines. The American colonies had federal inspection control over imported drugs starting in 1848. The FDA began in 1862 with a single chemist in the U.S. Department of Agriculture. In 1906, the Food and Drug Act came into effect, which began the modern era of the FDA by adding regulatory functions to the scientific mission. This act prohibits interstate commerce of misbranded and adulterated foods, drinks and drugs. Drug safety and labeling was not addressed in the act. After multiple name changes, in July 1930, the FDA, as it is still known today, came into existence. Although

significant, the Food and Drug Act had gaps. Some products legal under this act resulted in serious consumer harm, as well as sales of ineffective drugs, such as Banbar - a worthless cure for diabetes or Lash-Lure - an eyelash dye that blinded many women. Many foods were deceptively packaged or labeled: Radithor - a radium containing tonic that caused a slow and painful death, Wilhide Exhler – a falsely promised cure for tuberculosis and other pulmonary diseases, and finally, in 1937, Elixir Sulfanilamide - a new wonder sulfa drug containing a toxic chemical analogue of antifreeze which resulted in over 100 deaths, many of whom were children. These and many other similar instances resulted in the1938 passage of the Federal Food, Drug and Cosmetic Act (FD&C). The FD&C required new drugs to be tested for safety and efficacy, to receive approval before marketing, and to have adequate labeling for safe use. Medical devices and cosmetics were also included in the act. Equally important, the FD&C provided the FDA with enforcement tools, such as the authority to perform factory inspections and issue injunctions. Within two months of the passage of the act, the FDA identified many drugs that could not be labeled for safe use directed by the patient. These drugs would require a prescription from a physician. This began the major debate between the FDA, drug industry, and health practitioners over what required a prescription. In 1941, Sulfathiazole tablets killed and injured hundreds of people due to contamination, resulting in a drastic revision of the manufacturing and quality requirements leading to what would later be know as Good Manufacturing Practices (GMP). In 1962, the Kefauver-Harris Drug

Amendment passed. This amendment required the drug manufacturers to prove to the FDA the effectiveness of their products before marketing them. The amendment also required the FDA to assess the efficacy of all drugs introduced since 1938, transferred the regulation of prescription drug advertising, and established GMP for the drug industry. GMP later became known as current Good Manufacturing Practices (cGMP), referring to the current version. It also granted the FDA powers to access company production and control records to verify those practices. The FDA resided under many different agencies until 1980, when the FDA fell under its current home, the Department of Health and Human Services (Food and Drug).

The cost of non-compliance with FDA regulations is even greater than the cost of quality systems personnel and documentation for pharmaceutical companies. A few examples of FDA enforcement activities follow. In October 2000, Wyeth Ayerst received fines of $30 million for cGMP deficiencies. In October 2001, TAP Pharmaceuticals received fines of $879 million for conspiracy to commit violations of the Prescription Drug Marketing Act and Aventis Pharmaceuticals received $33.1 million in fines for submitting false information to the FDA. In May 2002, Schering-Plough, received a consent decree and $500 million in fines for cGMP deficiencies at its New Jersey and Puerto Rico manufacturing facilities. In 2003, the FDA approved Schering-Plough's cGMP repair plan. In 2003, Abbott Laboratories' Ross Products Division paid $600 million in fines to settle charges that it obstructed a criminal investigation into

sales of marketing of its patient feeding tubes and pumps. In 2004, Pfizer paid $430 million in fines for criminal charges to settle allegations that its Warner-Lambert unit caused doctors to submit Medicaid claims for unapproved uses of one of its drugs. The FDA enforcement statistics for 2002 are 13 seizures, 15 consent decrees of permanent injunctions filed, 372 arrests by the Office of Criminal Investigations (OCI), 317 convictions (OCI), 755 warning letters issued, 7,180 FDA-483s issued, 5,025 product recalls required, 18,572 inspections executed, 32,654 import refusals performed, $18,300,000 in asset forfeitures collected (OCI), and $24,027,549 in fines and restitution handed down (OCI) (Food and Drug). The cost of non-compliance is very expensive.

Today the FDA is a scientific, regulatory, and public health agency with significant enforcement powers that oversees items accounting for 25 cents of every dollar spent by consumers. The agency grew from a single chemist in 1892 to over 9,000 employees and a budget of $1.3 billion in 2001. The FDA moved from a product based inspection approach, to a systems based inspection approach in February of 2002 for drug inspections. Medical Devices moved to a systems based inspection approach in the mid 1990s. FDA enforcement powers have also increased significantly recently in order to protect the consumer. The FDA monitors the design, manufacture, import, transport, storage, labeling, advertising, performance claims, advertised risks, and sale of about $1 trillion worth of products annually that cost taxpayers about $3 per person (Food and Drug). Today drug consumers blindly take prescription and non-prescription

drugs knowing that the FDA ensures the identity, strength, quality, effectiveness, and purity of the drug.

Lean Thinking is a combination of the best processes and practices that optimize resources and yield the best product in the fastest time, at the lowest cost. Lean Thinking is an umbrella for “total quality management,” “continuous improvement,” “zero defect,” “six sigma,” “DMAIC,” and other similar terms. These concepts focus on doing the right thing, at the right time, in the right place, in the right quantity, and doing it right the first time. Lean is significantly different from traditional, internally focused, push production concepts and approaches of batch-and-queue manufacturing, with high inventory, long wait times, high backflow, and value defined by the corporation. Lean manufacturing focuses on single-piece flow, defining value from the customer’s view, elimination of muda, minimal inventory, using worker capabilities, fast cycle time, and cellular organization by product lines or product teams (product systems). One of the first flow thinkers was Henry Ford, with dedicated tools and the beginnings of integrated product development. Taiichi Ohno of Toyota in Japan developed many techniques for automotive production facilities. He focused on set-up time reductions, simplification of activities, and making a few parts instead of huge inventories resulting in quick identification of errors, thereby reducing the number of bad parts manufactured. Every employee had the ability to stop the production line when a problem occurred. He also emphasized and ensured a highly skilled, motivated work force, and focused on reducing muda. He established work

teams with full responsibility for housekeeping, minor tool repair, quality checking, and incremental or small improvements through collective thinking (kaizen) for a portion of the process. Ohno also instituted a problem solving system called “the five whys” to ensure the root cause was identified and eliminated permanently. Toyota offered lifetime employment, pay by seniority, instead of job function tied to profitability through bonuses. Rewards and advancement went to team players, instead of individuals displaying genius in a single area. In response, employees agreed to flexibility in work assignments and initiating improvements, instead of just responding to problems (Deming’s idea of “cooperation”). Finally, Toyota consulted directly with existing customers in planning new products. These actions and others resulted in nearly 100% yield and a drastic drop in rework and waste. These same techniques were applied to suppliers (partners) so that everyone benefited. As with most drastic changes in corporate focus and operations, the Chief Executive Officer (CEO) must support the lean approach (Womack, Lean Thinking, 2003).

Statement of the Problem

Compliance with FDA regulations in the manufacture of drugs and drug products is extremely expensive in the highly competitive pharmaceutical industry. Due to the importance of FDA regulations in protecting pharmaceutical and biologic consumers, and the FDA’s systems based compliance requirements to ensure this protection, pharmaceutical companies must have large complex dedicated quality systems. Quality systems constitute the firms’ programs to

ensure, verify and document compliance to cGMP, governing regulations, internal procedures, and specifications. Adequate systems to prevent and resolve difficulties during manufacturing are also required. All these activities result in extremely high overhead costs (millions of dollars in staff and documentation). These costs must be controlled and minimized. Lack of compliance to FDA regulations can cost millions and even billions of dollars through fines, warning letters, untitled letters (violations that are less serious than those addressed in a warning letter, but support future enforcement actions), injunctions, product recalls, product shipping holds, consent decrees, arrests, convictions, and facility closures. Therefore, compliance through effective and efficient quality systems is much less expensive than non-compliance. To ensure profitability of the company and retention of the ability to manufacture, distribute, and sell drugs, it is critical that the quality systems understand and address FDA inspection methods and compliance requirements.

This paper examines the application of Lean Thinking to pharmaceutical quality systems, defining the FDA as the customer. The product is defined as the deliverables required by the FDA. Lean Thinking provides an effective and efficient process for specifying value as defined by the FDA, and identifying and mapping the value streams (quality data and information required by FDA). Lean Thinking also focuses on making the value-creating steps flow and pulling the required information from the manufacturing process (including quality operations

in the manufacturing product cell). Finally, Lean Thinking strives to achieve perfection of process through continuous improvement.

Although compliance is much less expensive than noncompliance, any measures taken to minimize costs and the associated compliance risks benefit corporate profits and the shareholders. Lean Thinking provides an efficient and effective mechanism to minimize compliance costs and risks associated with the quality systems of a pharmaceutical manufacturer.

Purpose of the Study

The purpose of this study is to provide recommendations for organizational alignment guidelines using the Lean Thinking processes and techniques as applied to the quality systems within the pharmaceutical industry, defining the FDA as the customer. This includes identification of the quality systems components, their associated product lines or value streams, and their efficient and effective interaction with the customer, the FDA. The results should minimize the quality systems costs and satisfy the customer, the FDA, which should result in improved quality and profitability, producing a competitive advantage while maintaining compliance. A new or unique perspective and key departure from standard thought in this study is to apply Lean Thinking manufacturing process and techniques to quality systems and define the FDA as the customer, instead of the pharmaceutical or biologic consumer. From a quality perspective, the FDA is the customer, since pharmaceutical products cannot be manufactured, shipped and consumed without approval of the FDA. Also, the

quality systems products are generated to satisfy the FDA. Lean Thinking is a mechanism for efficiency, effectiveness, cost reduction and quality improvement. The quality systems components are identified and detailed as a result of the research and analysis of this thesis. The pharmaceutical quality systems assure overall compliance with cGMPs, other regulations, internal procedures, and specifications, including review and approval authority. It includes all product defect evaluations and evaluation of returned and salvaged drug products as per 21 CFR 211, subparts B, E, F, G, I, J and K. It also includes the review and use of the cGMPs for Finished Pharmaceuticals, 21 CFR 210, 21 CFR 211, and 21 CFR 314 to evaluate manufacturing processes (Food and Drug). Lean Thinking application to quality systems should result not only in corporate survival, but corporate growth as well, in an extremely competitive industry.

This thesis also provides additional focus on the change control system within the quality system with the FDA still defined as the customer. The change control system interacts intimately with all of the quality system functions and is also included in the Federal Food Drug and Cosmetics Act, section 506A and referenced in the Federal Code of Regulations (CFR), 21 CFR 314.70. It is also included in the Compliance Program Guidance Manuals (7356.002, 7356.002M), and evaluated during inspections. The change control system evaluates all changes (improvements are considered changes), modifications, and repairs to manufacturing facilities, major equipment, critical systems, and processes for their impact on product quality. This includes evaluation of changes relative to

compliance with existing validations, product license impact, submission to regulatory authorities and internally documented procedures.

I have found no studies relative to the application of Lean Thinking to quality systems in any industry, including the quality systems in the pharmaceutical manufacturing industry. There are also no studies identified relative to the development of an organizational structure or guidelines for the design and implementation of lean quality systems under FDA regulation. Many studies exist concerning the application of Lean Thinking to manufacturing operations. A few studies exist relative to the application of Lean Thinking to non-manufacturing and service functions, one of which is covered in the review of literature.

Theoretical Bases and Organization

This thesis covers the application of Lean Thinking to pharmaceutical quality systems. Through the application of Lean Thinking, the FDA must be viewed as the customer and the FDA deliverables viewed as the product. The third and most critical step in Lean Thinking is flow. Flow requires making all of the value-added activities flow efficiently and effectively with no wasted activities. If the FDA is not identified as the customer, then all of these activities become non-value added but required, and flow is sub optimized for a quality system by not focusing on these critical activities. The end user of pharmaceutical products consumes the drugs as prescribed by their physician without regard for documented evidence of quality or manufacturing compliance. This is because

the patient and physician both know that the FDA has approved the product for manufacture and sale. Additionally, the patient and physician know the FDA has executed audits of the manufacturing facility to ensure that the product complies with the required specifications and was manufactured under cGMP conditions. The FDA also verifies the associated validations, training, regulatory submittals, approved change control activities, and all supporting documentation.

There are studies relative to the application of Lean Thinking to non-manufacturing functions, such as finance, changing from cost based accounting to activity based accounting, product design, purchasing, planning and supplier management. There are also cases where Lean Thinking was applied to manufacturing operations and then administrative functions. Many of these cases have been reviewed for ideas in this study.

Limitations of the Study

The study is limited to satisfying the need of the customer, the FDA, relative to quality systems and the change control system within the pharmaceutical industry. Satisfying the FDA will help ensure unimpeded manufacturing output. It does not detail the regulatory affairs reporting requirements or quality operations within the manufacturing cell. Additionally, this study does not detail value stream identification of the following quality systems components: laboratory operations (including sample control, raw materials receipt and approval), supplier quality approval and contracts, training and qualification of employees, quality auditing, quality operations, management

review of the quality system, and annual record review. It is very beneficial to have already implemented Lean Thinking to existing, ongoing, already approved pharmaceutical manufacturing operations, which is not addressed herein. Preexisting lean manufacturing operations are critical in order to clearly understand the process and how to collect and organize the required information to satisfy the customer. Although the Lean Thinking process as applied to quality systems utilized in this study could be applied to additional areas such as new facilities, new drug development and approval, these applications are outside the scope of this study. Additionally, this paper does not address the defined product life cycle. However, manufacturing improvements within the product life cycle are addressed through the change control system and the quality systems, ensuring customer (FDA) satisfaction, therefore eliminating any restrictions to manufacturing operations.

Definition of Terms

Activity-based costing: A management accounting system that assigns costs to products based of the amount of resources used (including floor space, raw materials, machine hours, and human effort) in order to design, order, or make a product.

Adulterated Drugs: Products not made according to cGMPs render those products to be adulterated under the cGMPs and the FD&C, section 501. Actions that can be taken by the FDA when adulteration occurs range from voluntary action taken by the firm to regulatory actions taken by the FDA against the firm

and those responsible for noncompliance. The following is a list of actions in order of increasing significance, costs and “pain” to the firm: FDA-483, Recall, Warning Letter, Border Alerts, License Suspension or Revocation, Seizure, Consent Decree, Criminal Prosecution.

Batch-and-queue: The mass-production practice of making large lots of a part and then sending the batch to wait in the queue before the next operation in the production process.

Cells: Organization of all of the activities and or equipment required for a specific product line. The layout of machines of different types performing different operations in a tight sequence, typically in a U-shape, to permit single-piece flow and flexible deployment of human effort by means of multi-machine working.

Change Control: A formal system to ensure that changes are classified and evaluated for their effect on product quality, status of validation, status of submission to regulatory authorities, license impact, and existing documentation. Also evaluates new systems and equipment, as well as improvements and repairs to facilities, systems, and equipment.

Code of Federal Regulations (CFR): The CFR is the codification of the general and permanent rules published in the Federal Register (also includes proposed rules and regulations) by the executive departments and agencies of the Federal Government. In short, it is a compilation of all federal regulation that has been published in the Federal Register. As related to drugs, 21 CFR 210, 21 CFR 211, 21 CFR 314.70 are applicable.

Consent Decree: If a firm has repeatedly violated cGMP requirements, the FDA may make a legal agreement with the firm to force them to make specific changes, which is enforced by the federal courts. Usually, consent decrees include fines (disgorgements), reimbursements to the government for inspection costs, due dates for specific actions, and penalties for noncompliance. Consent decrees are usually permanent, but at times specified in the agreement when the firm has achieved compliance, it can petition the court to remove the decree (only two times since 1990). Most often the FDA will set up an office at the facility to oversee activities.

Critical Systems: Systems that are common to multiple areas of manufacturing, whose failure to meet quality requirements would have direct impact on product quality (ex. water for injection, reverse osmosis water, ultra filtration water, clean steam, alcohol system, process compressed gases, classified HVAC rooms, clean in place and steam in place systems, etc.)

Current Good Manufacturing Practices (cGMP): Regulations, guidelines, Human Drug cGMP notes, and accepted industry practices outlining the minimum standards for manufacturing practices for the production of drugs and biologics intended for humans and animals. cGMP regulations help the FDA enforce the FD&C by specifically listing requirements needed to ensure that products are manufactured in a state of control. As related to drugs, 21 CFR 210, 21 CFR 211 are applicable. cGMP regulations, which have the force of law, require that manufacturers take proactive steps to ensure that the products are safe, pure,

and effective. cGMP coverage includes a quality approach to minimize or eliminate contamination, mix-ups, errors, as well as record keeping, personnel qualifications, sanitation, cleanliness, equipment verification, process validation, and complaint handling. For international purposes, any reference to GMP should be understood as a reference to the current European community (EU) GMP (cf. Vol. IV of the Rules Governing Medicinal Products in the EU).

Cycle time: The time required to complete one cycle of an operation or the time required for completion of all the activities required to produce a product. If cycle time for every operation in a complete process can be reduced to equal takt time, product can be made in single–piece flow.

FDA-483: This is the form issued by the FDA that details observations of noncompliance with cGMPs during an inspection. Although firms are not required to respond to FDA-483s, it is considered prudent to do so, telling the FDA what will be done to correct the immediate specific problem and also, what will be done to correct the system(s) that are the root cause(s) of the problem. Failure to respond and comply will more than likely result in an increasing severity of enforcement actions.

Federal Food, Drug and Cosmetics Act (FD&C): As related to drugs, U.S. Code, Title 21, chapter 9, is a law passed in 1938, that grants the FDA power to regulate food, drugs, medical devices, cosmetics and biological products. Chapter 9, subchapter VII details the general authority as applied to drugs. Chapter 9, subchapter V, subchapters A, B, D, E, details the regulation of drugs and devices.

Flow: The progressive achievement of tasks along the value stream so that a product proceeds from design to launch, order to delivery, and raw materials into the hands of the customer with no stoppages, scrap, or backflows.

Food and Drug Administration (FDA): The FDA is a U.S. government agency that has been charged with the protection of public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping speed innovations that make medicines and foods more effective, safer, and more affordable. It also helps the public get the accurate, science-based information they need to use medicines and foods to improve their health. The FDA receives its powers from the FD&C. The FDA enforces laws on the manufacturing, testing, and use of drugs and medical devices. The FDA must approve a drug for marketing before it is made commercially available to the public.

Food and Drug Administration Modernization Act (FDAMA): The FDAMA, enacted 11/21/97, amended the FD&C relating to the regulation of food, drugs, devices and biological products. Section 116 of the Modernization Act added section 506A, which provides requirements for making and reporting manufacturing changes to an approved application and for distributing a drug product made with such a change.

Lean Thinking: A coordinated approach originating in manufacturing (mostly from Toyota) that is a combination of best processes and practices that optimize

resources and yield the best product, in the fastest time, at the lowest cost. It is an umbrella for “total quality management,” “continuous improvement, “zero defect” and other similar terms that focus on doing the right thing, at the right time, in the right place, in the right quantity and doing it right the first time. Lean thinking is externally focused, uses pull techniques, instead of push, focuses on single-piece flow, defining value from the customers view, and elimination of muda. It also focuses on minimal inventory, using worker capabilities, fast cycle time, and cellular organization by product lines or product teams (product systems), with step-by-step – activity-by-activity mapping of the defined value stream. Effective application of Lean Thinking results in significant increases in available space, production capacity, and cash flow resulting from reduced inventory.

Muda: Any activity that consumes resources but creates no value. Waste.

Perfection: The complete elimination of muda, such that all activities along a value stream flow and create value.

Pull: A system of cascading production and delivery instructions from downstream to upstream activities in which, nothing is produced by the upstream supplier until the downstream customer signals a need. A pull system is critical to the reduction or elimination of inventory.

Quality Systems: The quality system as defined by the FDA, assures overall compliance with cGMPs, internal procedures, and specifications. The system includes the quality control and quality assurance unit, and all of its review and

approval duties (e.g., change control, reprocessing, batch release, annual record review, validation protocols, and reports, etc.). It includes all product defect evaluations and evaluation of returned and salvaged drug products. As related to drugs, 21 CFR 210, 21 CFR 211, 21 CFR 314.70 are applicable.

Recall: Recalls are voluntary actions made by the firm to remove products from the market. The FDA cannot recall drugs; however, they can suggest to firms that they take action on “violative” or adulterated products. The FDA has three classes of recalls: I, II, III, with Class I being the most serious.

Single-piece flow: A situation in which products proceed, one complete product at a time, through various operations in design, order taking, and production without interruptions, backflows, or scrap.

Standard Operating Procedure (SOP): A written, approved, and controlled procedure detailing the required actions or activities for a specific function.

Transparency (visual control): The placement in plain view of all tools, parts, production activities, and indicators of production system performance, allowing the status of the system to be understood at a glance by everyone involved.

Validation: An approved formal methodology used for establishing documented evidence that provides a high degree of assurance that a specific process, product, piece of equipment, or software program will consistently produce a product meeting its intended predetermined specifications and quality attributes (suitability, reliability, accuracy).

Value: A capability provided to a customer at the right time at an appropriate price, as defined in each case by the customer.

Value-Stream: The specific activities required to design, order, and produce a specific product, from concept to launch, order to delivery, and raw materials into the hands of the customer.

Warning Letter: A warning Letter is a communication to the firm that has been reviewed by several levels of the FDA, including the district office and the Center at FDA's headquarters. The Warning Letter generally states that the firm has made products that are adulterated, violating the FD&C and that the firm has a very limited amount of time to address the problem(s) before the FDA takes further regulatory action against the firm, the adulterated product, and responsible individuals. Responses to a Warning Letter are required and are typically long, complex documents providing details and rationales for what the firm is planning to do. Warning Letters are also used by the FDA to communicate to the broader industry what the FDA believes is essential for compliance.

CHAPTER 2

REVIEW OF THE LITERATURE

Many books relative to Lean Thinking were reviewed to learn and understand the processes and techniques for application to pharmaceutical quality systems prior to a decision to focus on Lean Thinking (James Womack & Daniel Jones, 2003), Learning to See (Mike Rother & John Shook, 2003), Seeing the Whole (James Womack and Daniel Jones, 2002), and Lean Lexicon *(*The Lean Enterprise Institute, 2003). Many articles were also reviewed at many websites, but only one is presented here, “Creating the Course and Tools for a Lean Accounting System” (The Lean Enterprise Institute, 6/25/03). Finally, the FDA website (http://www.fda.gov/) was reviewed extensively, and is discussed. An extensive search of the Internet failed to reveal a single article applying Lean Thinking to quality systems or to quality systems under FDA regulation. The research and analysis for the application of Lean Thinking to pharmaceutical quality systems for this thesis is mainly focused on these books, the listed article, and the FDA website. Additional information sources are listed in the references.

Lean Thinking, by James Womack and Daniel Jones (2003), provides an excellent analysis of the differences between traditional manufacturing approaches and the Lean Thinking approach. It is a great starting point to understand Lean Thinking. They detail the advantages of the Lean Thinking approach and provide the reader a general understanding of the entire concept.

They cover the history, development, and current state of the Lean Thinking approach. They provide excellent descriptions and definitions of the five key principles and standard terminology of Lean Thinking. They also provide a detailed analysis covering a wide range of examples of corporations that have implemented Lean Thinking, from a bicycle manufacturer, to Pratt & Whitney, the largest manufacture of military jet engines, to the manufacturer of Porsches. They also provide an excellent action plan in Chapter 11 to provide an overview of the steps required to implement Lean Thinking in any corporation, along with their associated time frames. The notes section in the back is also very informative. They also provide some examples of non-manufacturing applications of Lean Thinking that were not very detailed and of little use for this thesis.

Although the book is an excellent starting point for understanding the entire concept of Lean Thinking from beginning to end, the book is not comprehensive to every detail for planning and implementation. Nor was it intended to be. Few, if any books can provide every detail for the implementation of a very complex process. To implement Lean Thinking, one would need to explore multiple sources of information on the subject (books, case studies, journal articles, etc.) and probably need the assistance of a sensei (consultant), as recommended in the book. The book does not cover the details of value stream mapping, but they reference the book, Leaning to See, by Rother and Shook (2003), total productive maintenance (essentially reliability engineering),

Kanban (regulation of the pull concept), and some other details of the Lean Thinking process. However, the book was invaluable to this reader and was utilized heavily in the development of this thesis.

Learning to See, by Mike Rother and John Shook (2003), is considered the standard for value stream mapping. Rother and Shook provide an outstanding detailed process for value stream mapping for the facility level, complete with diagrams and examples. They define value stream mapping and explain why it is an essential tool. They cover material and information flows, identifying product lines, and the responsible person of the value stream, including a job description. They detail the generation of a current value stream map, including paper size, icons to use, information to include in the icons, how to calculate the information for the icons, and provide an example of the process. They also detail what makes a value stream lean, generation of a future state value stream map, and how to achieve the future state value stream map, all covered in the detail referenced for the current value stream. Although reading other books, case studies, and articles on value stream mapping will always provide an improved understanding, provide additional nuances, and provide additional viewpoints, this book is detailed enough to execute and implement the value stream mapping activities. Even though a value stream was not actually mapped, an understanding of the process was required to identify the value streams and activities within a value stream, which made this was a very valuable book.

Seeing the Whole, by James Womack and Daniel Jones (2002), is considered the standard for extending the field of view of value stream mapping from raw materials to the end customer. It is an extension of the excellent book Learning to See, by Mike Rother and John Shook. Womack and Jones provide an outstanding detailed process for value stream mapping, complete with diagrams, charts, new mapping icons for extended value streams, and examples. They cover all the steps and time required to move a typical product from raw materials to finished goods in the hands of the customer. They also demonstrate the mapping method for demand amplification of orders as they travel up the value stream, steadily growing quality problems, and steadily deteriorating shipping performance at every point up the value stream from the beginning to the customer. They detail a realistic example of four corporations sharing a value stream creating a win-win current and future state for all corporations and the customer, including key problems in the shared value stream. They provide the implementing managers a step-by-step value stream mapping process that converts the traditional isolated value stream map, which compartmentalizes operations, into an ideal future state value stream, which allows value to flow from raw materials to the customer. This includes identification of key drivers of hidden connectivity costs upstream and downstream of the corporation, such as elimination of unnecessary transport links, inventories, and handoffs of materials, equipment, or supplies. Although reading other books, case studies, and articles on extended value stream mapping will always provide an improved

understanding, provide additional nuances, and provide additional viewpoints, this book is detailed enough to execute and implement the extended value stream mapping activities. It also provides the big picture of the ultimate goal, all corporations in a value stream working together in a win-win situation to satisfy and delight the customer. Even though an extended value stream was not actually mapped, an understanding of the process and big picture was required for the analysis performed. This is an excellent book.

The Lean Lexicon, by the Lean Enterprise Institute (2003), is the ultimate Lean Thinking dictionary, complete with an illustrated glossary, definitions, and examples of key Lean Thinking terms and concepts. The authors bring clarity to many Lean Thinking terms that are frequently misunderstood, misused, and create confusion. It includes the common terms, as well as new terms that may be unfamiliar to people new to the Lean Thinking approach. It is very helpful to see these terms, processes and concepts to help provide a complete picture of Lean Thinking. The dictionary was complied with the help of industry professionals implementing Lean Thinking. This book is a must for anyone implementing Lean Thinking.

"Creating the Course and Tools for a Lean Accounting System," (Lean Enterprise Institute), is a success article that provides an outstanding analysis of the benefits of Lean Thinking, as well as providing an excellent example of implementation of Lean Thinking in a non-manufacturing environment. The article involves a division of Parker Hannifin, a world leader in diversified

manufacturing, which has $6 billion in annual sales. The transition to a lean accounting system is critical and identified in Womack and Jones' book, Lean Thinking, as item number one of years three and four of the lean implementation plan. Parker experienced some of the same problems encountered in the application process that were encountered in this thesis application of Lean Thinking to non-manufacturing operations. Some of the problems encountered are customer identification, product identification, value stream identification, and application of flow and pull. Parker created an excellent lean accounting system that provided the required government reporting requirements, but also provided the manufacturing operations and support groups the actionable, timely information they needed to make effective decisions and understand the trends and performance of the operations. The article also clearly identifies the benefits of lean, thereby bringing clarity to potentially missed information in all the other lean books and articles reviewed. The benefits of Lean Thinking are increased cash flow from reduction in inventory, increased space from reduction in inventory and personnel, and increased manufacturing capacity. Failure to have a plan to utilize these newly available resources will eliminate much of the benefits of implementing Lean Thinking across the corporation. This article is a must for Lean Thinking implementation.

U.S. Food and Drug Administration website (http://www.fda.gov/) is a comprehensive website that was utilized extensively throughout the research and analysis of this thesis. The website was critical to the identification of value as

defined by the customer and to identify the value streams and their activities. It was also essential to understanding the background, history, evolution, enforcement actions, and authority of the FDA. The documents referenced below are critical to understanding the FDA authority, enforcement capabilities, regulations, inspection approach, and expectations relative to the pharmaceutical industry. This understanding is critical in order to extrapolate Lean Thinking to pharmaceutical quality systems and identify the required quality systems components and their responsibilities. The FD&C is chapter 9 of the United States Code (USC). The FD&C, chapter 9 (USC), subchapter VII clearly identifies the authority of the FDA to regulate, inspect, and levy enforcement actions on the pharmaceutical industry. The FD&C, chapter 9 (USC), subchapter V clearly identifies the federal governments expectations concerning the manufacture, packaging, and distribution of drugs, such as adulteration, contamination, etc. 21 CFR 210, 21 CFR 211, and 21 CFR 314 are the actual regulations derived from the FD&C that the pharmaceutical industry must comply with. Human Drug cGMP notes are notes to FDA personnel and industry concerning clarification of a regulation or expectation. They are also used to notify FDA personnel and industry concerning increased focus on a specific item or items. CPGMs, 7356.002, 7356.002M are generated and updated by the FDA to provide FDA interpretations of the regulation for FDA personnel and industry. Other critical FDA documents required for the research and analysis of this thesis: FDA Compliance for Industry, Changes to an Approved New Drug

Application or Abbreviated New Drug Application; FDA Guidelines on General Principles of Process Validation; Investigations Operations Manual (IOM); and the Regulatory Procedures Manual (RPM). The Office of the Commissioner (OC) and the Office of Regulatory Affairs areas of the website were critical to acquisition of the desired and required information for the FDA-Regulated Industry, and a complete listing of resources is available.

CHAPTER 3

METHODOLOGY

Design of the Study

This study applies the manufacturing processes and techniques of Lean Thinking to the pharmaceutical quality systems under FDA regulation. It is broken down into the five Lean Thinking principles referenced below. Each section begins with a discussion of the Lean Thinking application processes and techniques as defined for manufacturing. This is followed by an analysis of the application of those processes and techniques when the FDA is defined as the customer for the quality systems supporting the manufacture of pharmaceutical or biologic products. The product is defined as the deliverables required by the FDA to ensure compliance. According to the FDA's Compliance Program Guidance Manual (CPGM), 7356.002, assessment of the quality system is two phased. The first phase is to evaluate whether the quality system has fulfilled the responsibility to review, approve, and assure all procedures are adequate for their intended use relative to production, quality, and record keeping. The second phase is to assess the data collected to identify problems. The quality systems components identified in the value section and their associated responsibilities represent the expectations and requirements of the FDA. The FDA uses a systems based inspection approach for drug inspections. Per CPGM, 7356.002, focusing on systems, rather than individual product lines, will

increase efficiency in conducting inspections because the systems are applicable to multiple product lines. Therefore, organization of the quality systems as systems that cover multiple product lines benefits the FDA and the organization. The systems based approach is utilized by the International Standards Organization (ISO), the European Union (EU), in the form of Quality Systems Requirements (QSR), and the Quality Systems Inspection Technique (QSIT) utilized for evaluation of medical devices (see Washington Business Information--The Food and Drug Letter, 12/21/1; Washington Drug Letter, 3/19/04; Drug GMP Report, March 2004; Washington Drug Letter, 9/3/01). The global move from a regulatory approach, and the associated industry response, is to a systems based organization. The quality systems components required to ensure compliance are identified in the value section with an overview of the deliverables required by the customer. The required details within some of the systems are identified in the value stream section, since these details comprise the value stream. Lean Thinking can be summarized in five key principles designed to eliminate muda:

1) Precisely specify “value” by specific product
2) Identify the “value stream” for each product
3) Make the value “flow” without interruptions
4) Let the customer “pull” value from the producer
5) Pursue “perfection”

The meta-principle of Lean Thinking is responsiveness to change and waste minimization (Womack, Lean Thinking, 2003). A sixth section provides general but important information regarding Lean Thinking, application of Lean Thinking to a financial system, and a Lean Thinking implementation timeline.

Value

Value is defined by the customer (externally focused) and is only meaningfully expressed in terms of a specific product, that meets the customer's needs at a specific price and specific time. A common error in traditional manufacturing operations is to define value internally (internally focused) and, if the customer fails to respond, the product is modified or the price is adjusted or a different marketing strategy is tried. Lean Thinking must ignore existing assets and technologies and rethink the business on a product-line basis with strong dedicated product teams. It must also redefine the role of the technical experts and reevaluate where to create value for the customer (Womack, Lean Thinking, 2003).

Value as defined by the FDA (customer) for drugs is contained in five types of documents utilized by the FDA to ensure the manufacturers' products are safe, effective, have the identity and strength, and meet the quality and purity characteristics as intended: FD&C, 21 CFR and Federal Register, CPGMs, other manuals, and Human Drug cGMP Notes issued by the FDA, for the FDA and industry are available on the FDA website. The regulatory breakdown is as follows:

- FD&C, Chapter 9 (USC), subchapter VII, General Authority
- FD&C, Chapter 9 (USC), subchapter V, Subchapter A, Drugs, Devices
    - Subchapters B, Drugs for Rare Diseases or Conditions
    - Subchapters D, Dissemination of Treatment Information
    - Subchapters E, General Provisions Relating to Drugs and Devices
- 21 CFR 210: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General, revised April 2004
- 21CFR 211: Current Good Manufacturing Practice for Finished Pharmaceuticals revised April 2004
- 21 CFR 314: Supplements and other Changes to an Approved Application.
- 7356.002: FDA Compliance Program Guidance Manual, Drug Manufacturing Inspections, implementation date, 2/1/02 (effective date of the implementation of systems based inspections)
- 7356.002M: FDA Compliance Program Guidance Manual, Chapter 56, Drug Quality Assurance, Inspections of Licensed Biological Therapeutic Drug Products, implementation date, 10/20/03 (covers the transfer of many of the Biological Therapeutic Drug Products to CDER)
- FDA Compliance for Industry, Changes to an Approved New Drug Application or Abbreviated New Drug Application
- FDA Guideline on General Principles of Process Validation
- FDA, Office of Regulatory Affairs, Investigations Operations Manual (IOM)

- FDA, Office of Regulatory Affairs, Regulatory Procedures Manual (RPM)

According to the FD&C, the Federal Register and the CFR must be used together to determine the latest version of a given rule. As an aid to industry and FDA personnel, CPGMs are designed, updated and published by the FDA and are intended to help industry interpret the intent of very complex and sometimes general regulations. Although the CPGMs do not have the force of law, they are derived from the FD&C and CFR, which do have the force of law. Since the FDA is the customer, these documents define customer value. In accordance with the FDA documents referenced above and industry standards, the following quality system components, along with an overview of their objectives, are identified as critical to ensuring compliance:

- Batch Release: assembles required components of batch files: run-sheets, laboratory testing data, all closed deviation reports, change control documentation verifying no repair and change activity impact, raw materials inspection and testing documentation and approval, ensures no critical systems failures, verifies quality review signatures present, closure of applicable reports or files, ensures compliance with product specifications, ensures packaging and labeling specifications are met, and quarantine of non-compliant materials and products,

- Quality Documentation: ensures documents and SOPs are controlled and approved, ensures revised documents have approvals and training documentation prior to issuance. Also maintains a document tracking system and ensures biennial review of SOPs verifying appropriateness to the current, validated state of the systems,

- Discrepancy and Failure Investigations: generates, tracks, trends, approves, ensures consistency, monitors effectiveness of corrective actions, evaluates product impact, and files all investigations across

all product lines for deviations to: written procedures, testing specifications, calibration requirements, SOPs, run-sheets, laboratory in-process and final product failures, environmental monitoring failures, calibration failures, critical systems, etc. Also includes stability failure investigations with field alert evaluations, corrective actions and preventive actions (CAPA), complaint reviews (quality and medical), rejects, and returns and salvages assessment, investigation, and disposition,

- Change Control: evaluates and approves proposed minor, moderate, and major changes to specifications, test procedures, raw materials, facilities, critical systems, support systems, equipment, computer systems (hardware, software), control systems, process steps, packaging materials, and label changes relative to the validations, regulatory submissions, license impact, current written documentation and product quality (identity, strength, purity, potency, safety, efficacy). Also approves implementation of new equipment and systems, as well as evaluates, approves, and determines quality release requirements for repairs to facilities, equipment, and systems that could impact product quality,

- Validation: ensures that an approved formal methodology is used for establishing documented evidence that provides a high degree of assurance that a specific (suitability) process, product, piece of equipment, or software program will consistently (reliability) produce a product meeting its intended predetermined specifications and quality attributes (accuracy). A process can only be validated after all the equipment and ancillary systems of a given process have been qualified and linked together. Also includes material qualification,

- Laboratory Operations: ensures that validated, approved testing methods (assays) are used for the analysis of raw materials, in-process product test samples, and final container product test samples. Also ensures that any test result failures are investigated and documented, such that a determination can be make as to the impact of the failure on product quality. Also includes subcomponent, metrology operations, for maintaining, tracking, trending, calibration and recalibration at the required intervals for all equipment and systems used to measure quality indicators (ex. on-line analytical instruments, flow meters, laboratory equipment, gauges). Laboratory operations also include subcomponent, raw

material receiving and release, to ensures that all raw materials are purchased from approved and qualified suppliers. The incoming materials are quarantined upon receipt until applicable testing and inspections are performed as required. A tracking and or lot number is assigned and the material is released or rejected accordingly. Reporting through laboratory operations is the sub component, sample control, which ensures traceability, labeling, storage and storage conditions, and distribution to the appropriate laboratory of all samples collected for analysis (in-process product, final container, raw materials, stability). This component is not detailed in the following sections,

- Training and Qualification of Employees: ensures that all employees are trained or qualified and that documentation exists, as required for their assigned training requirements (including required periodic cGMP training) and that retraining occurs at the specified intervals. Also ensures that the required training on revised and new documentation occurs prior to issuance of the documentation. Another critical function is training all trainers on how to train personnel to ensure consistency of training. This component is not detailed in the following sections,

- Supplier Quality Approval and Contracts: ensures the supplier meets the quality systems requirements per the FDA and ensures contracts are generated and signed to clearly document specifications or other parameters as required. The contracts also require notification to the company relative to any changes made to the quality systems documentation, material formulation, manufacturing processes or a change in the raw materials used by the supplier. This component is not detailed in the following sections,

- Quality Auditing: schedules and performs audits of, all internal facility departments, contractors, and suppliers to verify compliance with internal and external SOPs and regulatory requirements. Also generates audit findings and reports of the audits that require responses to the findings in the form of corrections, corrective actions, preventive actions, effectiveness monitoring criteria and associated dates for completion. This component is not detailed in the following sections,

- Annual Record Review: ensures annual review of a representative number of batch records for each product line with trends identified. Also analyzes and verifies key quality indicators relative to the specifications, SOPs, and other associated documentation. This component is not detailed in the following sections,

- Management Review of the Quality System: ensures senior management review of the quality systems and all systems for suitability, adequacy, and effectiveness at regularly defined intervals. It also includes review of quality and performance indicators for manufacturing and all other support functions. This consists of the review, analysis, trending and tracking of the quality and performance indicators for each quality system component. It also includes reviewing new or revised regulations that may have an impact on the business or quality system. It also includes evaluation of recalls, field alerts, audit responses, incidents reported to regulatory agencies, and product complaints and trends. All information discussed is documented; however, regulatory agencies only have the authority to verify that the review has occurred (dates), the meeting attendees, and that management has exercised due diligence in executing their responsibility for the quality systems. Action items or CAPAs are issued to address negative trends, system failures, system inadequacies, and new system requirements. Action items or CAPAs from previous meetings are addressed along with the current information. This component is not detailed in the following sections,

- Quality Operations: works within the manufacturing cells and ensures verification and approval of production activities, compliance to approved SOPs, and supports change control in maintaining control relative to repairs, improvements, validations and other changes within the manufacturing cell. Quality operations also evaluates deviations real-time relative to continuance of manufacturing operations of a given batch or lot. Quality operations also provides support to manufacturing relative to knowledge concerning quality systems requirements, compliance requirements, current regulations, and provides training as required. Quality operations also provides guidance with all operational decisions concerning manufacturing operations and product quality, ensures that the manufacturing run sheets are compete and reviewed prior to document release to batch release, ensures any deviations are initiated and documented, and

manages the pest control monitoring program. This component is not detailed in the following sections.

In addition to the information and systems required above, the FDA wants the information to support and verify the previously referenced regulations and wants the information at specific times (such as during audits, pre-approval of a process or analytical assay, CBE-0, CBE-30, annual report, upon request, etc). The FDA requires the information at any cost; therefore, cost adjustment is not an option in this application, although the corporations must minimize cost. Many quality systems will attempt to provide additional information in place of the required information, which is one reason why the FDA has an increasing number of enforcement actions. A product line, from a quality systems perspective, would be a designated value stream responsible for a customer (FDA) deliverable.

Value Stream

The product value stream consists of the steps and processes required to bring a specific product from raw materials to finished product in the hands of the customer. Analysis of the entire flow of a product reveals enormous waste and non-value added activities, frequently referred to as process reengineering. In general, there are three types of activities that occur within a value stream: value-added activities (or value creating activities); non-value added activities (or non-value creating activities) that are required and unavoidable due to current technologies, production methods, assets and equipment, or regulations; and non-value added activities that do not create value and are avoidable (Womack,

Lean Thinking, 2003). Identifying the non-value added and avoidable activities is the most demanding and also provides the first and easiest target for elimination. The identification process of non-value added activities requires input from the workers, who have daily experience with the details of execution, and could also reveal many of the common causes of variation. Root cause analysis and other quality improvement tools (six sigma, DMAIC, SPC, etc.) assist in the elimination or repair of common cause variation, which results in a tighter (smaller standard deviation), more stable (predictable) process. It is important to keep in mind that the entire organization must be analyzed to improve the value stream as a whole. The culmination of the value stream analysis is a current and future state value stream map, activity-by-activity and step-by-step, by product family. Learning to See, by Mike Rother and John Shook provides a detailed analysis and execution of value stream mapping. Focusing on customer value, eliminating muda, monitoring and trending key quality and performance indicators, and continuous improvement of the value stream will automatically produce a competitive position. As Womack and Jones stated in their book, Lean Thinking, “To hell with your competitors; compete against perfection by identifying all activities that are muda and eliminating them” (p. 49).

The value streams for the quality systems components, with the FDA defined as the customer, and the product defined as the FDA required deliverables, consists of multiple value steams for each quality component. Some examples of value streams derived from the previous analysis of value are

examined and documented as a list of requirements or value-added steps needed to ensure compliance or satisfy customer value. Quality systems components, batch release, quality documentation, discrepancy and failure investigations, change control, and validations have been chosen for the purposes of this thesis. Each component is listed below with the required value streams identified and detailed instructions of the activities required for one of the value streams:

- Batch Release: This component consists of a value stream and sub-value streams as appropriate for final batch record review and approval (relative to destination), review and approval of manufacturing run sheets, review and approval of required forms, ensure compliance with product specifications, closure of discrepancy investigation reports, closure of other investigation reports (out-of-specifications, out-of-tolerance, out-of-limits, etc.), collection and review of test results (in-process and final container), collection of environmental monitoring testing, collection and review of critical systems information, collection of raw materials inspection and testing information, collection of change control reports relative to repair or modification work on major equipment and critical systems, collection of equipment cleaning documentation, verification of expirations dates of materials used, labeling specifications and other printed materials. The value stream for a final batch record review is detailed by the following value added activities:

    - Review all documentation for compliance with Good Documentation Practices,

    - Verify that all product, reagent, and buffer manufacturing run sheets and forms are present, and verify all required signatures,

    - Verify all major equipment use, cleaning and maintenance documentation is present, and verify all required signatures,

- Verify that all raw materials inspection reports and verification testing results are present and within specification, and verify all required signatures,

- Verify that all required in-process conformation and targeting test results from all applicable laboratories including microbiology are present and within specification, and verify all required signatures,

- Verify all microbiological environmental monitoring is present and within specification, and verify all required signatures,

- Verify that all room and major equipment temperature charts are present and within specification, and verify all required signatures,

- Verify that all room humidity and differential pressure charts are present and within specifications, and verify all required signatures,

- Verify that all filling, packaging, and labeling run sheets are present, and verify all required signatures,

- Verify all part numbers, quantities and lot identifications are present, and verify all required signatures,

- Verify overall rejects against packaging inspection documentation is present, and verify all required signatures,

- Verify number of units packaged against the lot accountability record report is present, verify all required signatures,

- Verify that all required change control reports are present, and verify all required signatures,

- Verify that all investigation reports for discrepancies, deviations, testing failures are closed, present, and verify all required signatures,

- Verify all critical systems cleaning, maintenance, and use documentation is present, and verify all required signatures,
- Verify that there are no deviations relative to the Bill of Materials, and verify all required signatures,
- Verify that all product specifications have been met for the designated distribution, and sign to verify,
- Verify that all labeling specification have been met for the designated distribution, and sign to verify.

- Quality Documentation (QD): This component consists of a value stream and sub-value streams as appropriate for new document generation, revision of existing documentation, and obsolescing of documentation for minor, moderate and major classifications. A tracking, numbering, and storage system are also required to ensure all documents meet the biennial review requirements, as well as meet the required storage and traceability requirements. Examples of controlled documents are: SOPs, forms, templates, Product Specifications, Bill of Material, Label Specifications, Protocols, drawings, manufacturing run sheets, and others. The value stream for a minor revision to existing documentation is detailed by the following value added activities:
  - Make all the desired changes to the controlled document with a single line through the portions to be deleted,
  - Provide hardcopy and electronic copy (with track changes),
  - Generate a report documenting evaluation of change impact to other documentation that may require revision,
  - Provide documentation of a detailed breakdown of each change to the document along with a supporting justification and possible supporting data,
  - Identify the change to be minor, moderate, major,

- Identify if training is required prior to document release,

- Obtain required signatures from quality cell manager, department owner, and document owner to process the document,

- Submit package to change control for moderate and major changes, for signature, which evaluates potential impact of change to validation, regulatory submission, customer notification, laboratory information systems updates, and other documentation, and moderate (requires co-release with another document or activity), or major (requires completion of the change control process for validation, customer notification, etc., prior to further processing),

- Submit package with associated forms to QD for minor change, along with the change package for any required associated document changes,

- Process the requested change along with the change package for any required associated documents,

- If no training is required, post the completed change copy for review approval signature,

- If no training is required, the controlled document is released and the package is filed accordingly,

- If training is required, post the completed change training copy for review approval signature,

- If training is required, ensure the required personnel is trained and documented,

- If training is required, submit training documentation to the training department and obtain the training department signature for release of the document,

- Submit the document package with all associated signatures and QD releases the document for use with a new revision number and effective date,

- For moderate and major changes, a second signature from change control would be required to release the document for use.

- Discrepancy and Failure Investigations: This component consists of a value stream and sub-value streams as appropriate, for discrepancies, stability failures, field alert evaluations, CAPAs, and returns and salvages. Out-of-specification, out-of-limits, and out-of-range may be handled by laboratory operations. Out-of-tolerance may be handled by metrology. The Value Stream for deviation investigations is detailed by the following value added activities:

  - Clearly define the problem, including the scope and depth (specific values, limits, how it happened, what was the requirement, what was the deviation, procedure number, issue date, section),

  - Provide a clear linkage to supporting documentation,

  - State the situation with few questions for clarification,

  - Include process flow diagram for clarity, as appropriate,

  - Take appropriate containment actions and document,

  - Provide rational for continuing manufacturing, included as appropriate,

  - Categorize risk assessment (minor, moderate, major),

  - Clearly state the rational for risk classification,

  - Notify appropriate management for major risks,

  - Notify regulatory agencies in a timely manner, as applicable,

- Notify customers in a timely manner, as applicable,
- Provide justification for risk assessment modification, if applicable,
- Assess the impact of any changes that have been performed and determine and evaluate for negative impact,
- Clearly state the investigation plan or SOP,
- Identify members of the investigation team and their qualifications,
- Clearly identify the owner of each activity,
- Clearly identify the overall owner of the investigation,
- Document Investigation steps and results,
- Revise and document plan revisions during the investigation as appropriate,
- Clearly document corrections to address the deviation,
- Provide a clear rational for corrections that were made,
- If no correction made, provide rational to support the lack of action,
- Thoroughly evaluate and document the effect of the issue on the product, process, and or system,
- Thoroughly evaluate the impact on related products, processes, and or systems,
- Evaluate if upstream and downstream product lots for impact relative to purity, safety, efficacy and stability,

- Identity and evaluate all affected lots with supporting by data,
- Investigate or determine as part of a trend or isolated incident,
- Consider potential for multiple causative factors,
- Thoroughly evaluate potential root cause(s),
- Clearly statement of root cause(s) and ensure it is not just a restatement of the problem statement,
- If no root cause is determined, provide adequate justification,
- State the methods utilized for root cause analysis,
- Include data to support conclusions,
- Ensure corrective actions correspond directly to root cause,
- Extend corrective actions to related potential product, process, and or systems,
- Derive corrective actions from a root cause analysis,
- If corrective actions result in a CAPA, record number,
- Clearly identify methods to measure effectiveness of corrective actions over an extended period of time,
- Clearly state acceptance criteria for effectiveness and demonstrate effective prior to file closure or CAPA opened,
- Ensure system is in place for the management and tracking of effectiveness of the identified corrective action,
- Provide evidence to support and prove implementation of all corrective actions,

- If feasible, verify the effectiveness of corrective action prior to implementation (ex. prospectively validated),
- Ensure the corrective action has no adverse effect on other products, processes or systems,
- Identify preventive actions and provide evidence to support or prove implementation,
- If feasible, verify effectiveness of preventive action and or validated prior to implementation,
- Make report a stand-alone document, complete and understandable,
- Clearly identify all sources of information,
- Ensure clear linkage of information to original data source,
- Make document flow support investigation process and element of investigation,
- Complete investigation in a timely manner,
- Ensure conclusions are supported by data collected with validated methods (not assumptions or speculation),
- Provide data to support effectiveness of actions taken,
- Ensure conclusion statement clearly defines impact to patient, product, process, system, critical systems, etc.,
- Clearly document product disposition,
- Assemble the summary of events in chronological order,
- Ensure closure statement clearly documents overall results, how the cause was identified and confirmed, actions taken,

improvements made, and trend result with no speculation, assumptions, or guesses,

- Ensure investigation and report comply with governing procedures,
- Verify all identified questions and issues are addressed,
- Consider regulatory, patient, and safety concerns,
- Provide clear and justifiable rationale for decisions,
- Ensure documentation of any extensions required for closure,
- Verify all required signatures present and close file.

- Change Control: This component consists of a value stream and sub-value streams as appropriate for minor, moderate, and major changes. There are value streams for repairs, changes or modifications, and new introductions of: manufacturing equipment, control systems, critical systems, support systems, facilities in manufacturing area, room classification changes, environmental controls, materials, material inspection requirements, procedures, batch records, forms, software, hardware, manufacturing processes, moving manufacturing processes within the facility, testing specifications, testing methods, drawings, product specifications, product label specifications, packaging specifications, supplier contracts, and other systems. The value stream for major change to a manufacturing process using a new piece of major equipment is detailed by the following value added activities:

  - Generate a change request detailing the current situation, proposed change, impacted product and justification for change,
  - Obtain required signatures and submit to change control,

- Present proposed change to the Change Control Board (management representatives of regulatory affairs, change control, engineering, environmental health and safety, director of manufacturing, validations, quality auditing, laboratories, technical support, quality operations, and the director of quality).

- Evaluate and identify as required or not required all of the following items at the change control board meeting:

    - Environmental health and safety impact,

    - Validation (process, cleaning, equipment, computer systems, facilities, other systems),

    - Calibration,

    - Computer 21 CFR 11 assessment (electronic records, electronic signatures),

    - Material qualification,

    - Material evaluation,

    - Supplier approval evaluation,

    - Global pathogen safety,

    - Stability evaluation,

    - Document changes,

    - Regulatory assessment relative to regulatory authority (global) submissions (pre-approval, changes being effective - 0 days, changes being effective – 30 days, annual reportable, medical approval),

    - Notification of affected customers (requires notification and approval of marketing),

- Notification of other affected facilities,
- Other studies as determined.

- Determine acceptance of proposed change and target completion date,
- Obtain signatures of all required change control board members,
- Validate equipment, cleaning and re-validate process, verify that no negative impact exists (related equipment, environmental monitoring, any downstream products) and include signed validation packages in the change package,
- Validate computer system or PLC if required for equipment operation,
- Generate stability data, probably with accelerated aging stability test results, as applicable, for release of product produced with the new process,
- Generate all required new documentation (procedures and forms for operation of equipment and training documentation, cross-reference of new process validation in existing validation package), procedure revisions (manufacturing run-sheets, etc.), regulatory submissions with approvals as required (i.e. pre-approval) from all applicable countries associated agencies, customer and other facility notifications, stability requirements, material qualifications, new drawings and updates, and include in change package,
- Generate post-approval effectiveness assessment plan including predetermined specifications for quality indicators, duration of effectiveness monitoring, and responsible personnel for monitoring,
- Assemble all required information and verify all approval signatures in the change request package and obtain required signatures to set the effective date of change (first potential date of use),

- Document the implementation date of change (date change was first used in process),
- Include signed post-approval effectiveness,
- Close and file the change request package.

- Validation: This component consists of a value stream and sub-value streams as appropriate for new introduction and modifications, for major equipment (some support equipment), computer systems (hardware and software), control systems, critical systems, processes, cleaning, material qualification, and analytical methods (see laboratory operations). A protocol must be completed and approved, including how the qualification and validation will be conducted including but not limited to predetermined acceptance criteria for test parameters (data collection methods must be validated prior to data collection), product characteristics, manufacturing equipment, decision points on what constitutes acceptable test results, identify appropriate number of replicate runs to demonstrate reproducibility, determine an accurate measure of variability, determination of upper and lower limits, normal operating conditions, worst case conditions, suitability of materials, calibration frequency, required maintenance activities and frequency, cleaning (frequency, testing verification, expiration), spare parts list, and performance and reliability of equipment or system. An associated final report must be generated and approved after completion of the validation activities. It includes, final results, conclusions, and deviations encountered in the execution of the protocol. Ultimately, confirming that the requirements identified on the validation protocol are met. The value stream for new equipment validation is detailed by the following value added steps:

- Prepare a validation plan to ensure an adequate understanding of equipment and process knowledge and consider all the following:
    - User requirements specifications,
    - Multi-functional team responsibilities,

- Analysis tools (Failure Mode and Effect Analysis, Design of Experiments, Analysis of Variance, Cause-Effect, mistake proofing, stability studies, capability studies, etc),
- Materials and components specifications and qualification,
- Product design specifications and pre-determined acceptance criteria,
- Product characteristics and methods for monitoring,
- Process flow diagrams or maps,
- Operating parameters (equipment, process) input, desired outputs and monitoring,
- Process capability and stability studies,
- Utilities, critical systems, equipment identification,
- Equipment capacity and safety,
- Equipment documentation, maintenance and calibration,
- Process operating documentation (manuals, operating procedures, SOPs),
- Personnel training and competency, including cGMP,
- Validation approach,
- Vendor selection, assessment, approval and purchase orders,
- Computerized systems validation status,

- Microbiological validation status,
- Analytical method (assay) validation status,
- Facility, utilities, ancillary systems validation status,
- Regulatory reporting requirements for all countries,
- Load capacity analysis for utilities,
- Equipment design and materials, and regulatory compliance requirements,
- Ensure appropriate signatory approvals.

- Perform an installation qualification (IQ). The IQ objective is to demonstrate by approved documentation that the equipment and ancillary systems are installed correctly (properly and safely). Verification documentation resides in the equipment qualification final report and addresses the review of the following attributes or provides supported documented justification for any items not performed:
  - Identify equipment design criteria and requirements,
  - Provide description of major system components,
  - Include equipment manuals and manufacturers installation requirements,
  - Identify the materials of construction with special attention to product contact areas,
  - Generate drawings for major equipment and critical systems including wiring diagrams,
  - Identify the utility requirements (electrical, compressed gases, cooling, heating, etc.),

- Identify the required spare parts list,
- Identify the preventive maintenance requirements including activities performed and frequency to avoid failure,
- Identify the equipment required environmental conditions (temperature, humidity, venting requirements, etc.),
- Identify the impact of the equipment on the room environmental conditions (heat, particle, waste generation),
- Identify the potential impact on other related, connected or involved systems.
- Identify equipment safety features,
- Generate a checklist of the identified requirements and perform installation verification,
- Ensure appropriate signatory approvals.

- Perform an operational qualification (OQ). The OQ can be completed concurrently with the execution of the IQ phase. The OQ objective is to demonstrate by objective evidence that the manufacturing equipment and ancillary systems perform as intended throughout the anticipated operating ranges. The OQ verifies the functional specifications. Verification documentation resides in the equipment qualification final report and addresses the review of the following attributes or provides supported documented justification for any items not performed:
  - Generate written draft equipment procedures (SOPs) detailing operation (including start-up, shut-down, key features, operational safety features), calibration, maintenance, cleaning, and frequency of each, with approval signatures,
  - Generate drawings and diagrams,

- Generate manufacturing run sheets to follow for operation and recording of the key operating parameters, with approval signatures.
- Perform any software or control systems validation,
- Identify cleaning validated cleaning requirements,
- Perform functional testing including worst-case conditions,
- Perform and document personnel training,
- Document inclusion of the equipment into the preventive maintenance, calibration, and change control systems,
- Ensure appropriate signatory approvals.

- Perform a performance qualification (PQ). The PQ can be completed concurrently with the execution of the OQ phase or may not be required if there is no difference in key characteristics of the materials being processed with the equipment (viscosity, density, stickiness, etc). The PQ objective is to demonstrate by objective evidence that the manufacturing equipment and ancillary systems perform consistently as intended throughout the anticipated operating ranges. It essentially verifies the user requirements specifications. Verification documentation resides in the equipment qualification final report and addresses the review of the following attributes or provides supported documented justification for any items not performed:
  - Confirm critical process parameters operating range,
  - Confirm repeatability, reproducibility, accuracy, precision,
  - Ensure appropriate signatory approvals,
  - Issue all SOPs, manufacturing run sheets, drawings, etc.

- Perform the process validation (PV) is now ready to be performed. The detailed activities are not be covered; however, an overview of the objectives are provided. The PV objective is to demonstrate by approved documentation that the process worst case or extreme operating limits are verified. Develop process parameters at production scale using product or product simulate under worst-case process conditions. A minimum of three consecutive, successful, production runs are required to complete the validation. All key process control limits and their sources and any justification linking the small-scale studies to production shall be included in PV documentation.

- Submit the completed and approved equipment qualification and validation and associated process validation to change control for inclusion in the associated change package. Validation is only one component of the requirements for implementation.

The value stream activities listed for each of the above quality systems components represent the basic required activities in order to maintain compliance with the value definitions previously identified. There are additional value streams within each quality systems component and these quality systems components are just a sample of the twelve quality systems components from the value section. Many of the value streams can be broken down to a higher level of detail, resulting in one or more sub-value streams. The analysis of the value streams across the entire organization starts with the inspection, testing and documentation of incoming raw materials, to the first production activity, in-process testing, final container testing, batch review, closure of deviation reports, closure of all quality impacting changes and repairs, and finishes with all documentation in the hands of the FDA. In most pharmaceutical companies, post-production activities constitute about two-thirds of the total product cycle

time from raw materials to the hands of the customer. In reality, these activities are what define quality and value, and demonstrate product compliance for the FDA; and, therefore, the manufactured product consumer. Due to the complexity and criticality of the quality systems components value streams, and the fact that much of the required information comes from manufacturing operations, it is very beneficial for manufacturing to be lean prior to the application of Lean Thinking to quality systems. If the FDA is not defined as the customer, then all of the quality documentation, review, approval and verification activities are defined as non-value added and flow will be lost. Additionally, it is critical that customer value frequently be reviewed and revised as necessary to consistently satisfy the customer over time and maintain focus on the customer. This is another critical reason for defining the FDA as the customer and the product as the required FDA deliverables for pharmaceutical quality systems.

Flow

Flow may be the most important concept of Lean Thinking. Flow can be introduced in any activity, but without consideration of the other four principles of Lean Thinking, the same level of muda can occur. Prior to a focus on flow, customer value has to be precisely specified, the entire value steam for a specific product line throughout the whole of the organization has to be mapped, and all of the avoidable non-value added steps have to be eliminated. Next, all the remaining steps and processes are organized to create flow. The concept of flow may be the most significant departure from traditional manufacturing organization

and thinking. The most common and prevalent organizational structure is by functions or departments, with the assumption that activities should be grouped by type of activity for focus, efficiency, measure and ease of management. Along the same line of thought, it would make sense to produce in batches. However, this approach creates wait times (bottlenecks) while the product waits for the next operation or for the departments to changeover (set-up) for the next operation. Traditional manufacturing thought is that this approach keeps everyone busy, maximizes equipment efficiency and reduces the number of changeovers or set-ups. This approach results in sub-optimization of resources and product output, and encourages managers to focus on optimization of their department, instead of optimization of value-creating activities throughout the entire value stream and facility. The recent manufacturing reengineering movement has realized the above problems, but has failed to coordinate the disconnected and aggregated processes. It has also failed to effectively address the impact on the remaining employees, which results in subtle sabotage by employees, deterioration of employee morale, and regression of the process after the reengineers are gone. Flow is easiest to recognize in the manufacturing area where it began, but can be introduced in any activity (same principles). Lean Thinking puts the focus on the product and its needs, rather than the organization or the equipment, such that all the activities needed to design, order, and produce a product occur in a continuous flow. Lean Thinking also redefines the work of functions, departments, and firms, resulting in positive employee contributions to value-

creating activities. It is also necessary to address the real needs of employees along the entire value stream, so it is in the employee interest to make value flow. Proper, effective, and constant communication in the beginning is critical no matter what program is being put in place. Employee reduction and corporate commitment to the employees should be addressed up front as well (Womack, Lean Thinking, 2003).

For the FDA, the quality systems components identified are organized as departments, functions, or systems because the FDA audits these areas as systems within the quality systems. The FDA utilizes the system based inspection process to ensure that the same level of control and quality occurs consistently across the entire organization within each manufacturing cell (product line). Failure to organize in a systems structure will result in longer audits because each manufacturing cell will have to be audited for all the quality systems identified. Additionally, the FDA will have to compare the quality systems of all manufacturing cells in order to ensure consistency across the organization. Failure to organize in a systems structure will also produce unnecessary redundancy of personnel and activities. However, the quality systems value streams must be made to flow. It is important to keep in mind that the quality systems products as defined here consists of the deliverables required by the FDA to ensure compliance. The key to flow for the purposes of this paper is to minimize total quality systems product cycle time, which will minimize the manufacturing product cycle time while still satisfying the quality system

requirements. On average, two-thirds of the manufacturing product cycle time consists of post-production activity. Additionally, it is critical to ensure that the manufacturing cells produce the required information in a form that will not have to be modified to satisfy the quality system requirements. The quality systems flow must be considered from the first action of any procedure or process, regardless of the department, to the final product in the hands of the FDA. Failure to do this will result in re-work of the information (back flows) and also generate backlogs (inventory) in the quality systems products. The focus is on the elimination of wait times and inventory in the quality systems product stream. The primary quality systems components affecting manufacturing cycle time flow for a current process are: discrepancy and failure investigations, change control, laboratory operations (including raw material receiving and release, and sample control), and batch release. A significant concept of lean thinking is continuous improvement. The primary quality systems components affecting improvements are: validations, change control, quality documentation, and training and qualification of employees. Finally, the quality systems components affecting continuing operations and compliance requirements are: management review of the quality systems, change control, quality documentation, discrepancy and failure investigations, laboratory operations, training and qualification of employees, supplier quality approval and contracts, quality auditing, and annual record review.

Quality Systems flow results in a focus on providing consistency of FDA deliverables across multiple manufacturing cells in a timely manner. Therefore, all the quality systems components must have flow. Additionally, there is an intimate interlinking of the quality systems components and manufacturing cellular operations. If the interactions are analyzed properly with lean thinking and made to flow, reductions in manufacturing product cycle time and quality systems documentation time will occur, and employee frustrations will be reduced. This will occur by ensuring that all required information, documentation, and resources are available as required to meet the business and quality needs of the organization. The quality systems components value stream steps discussed earlier are now examined.

Flow, from the batch release perspective, relative to the value stream discussed means that all the required documentation for release of the manufactured products is complete and organized in the batch file as soon as possible after the manufacturing is complete, with no wait times. Many employee frustrations in the value stream result from the need to ship product as scheduled; however, open reports require closure, documentation corrections require completion, and required information has not been submitted. If release of product is not predictable, it is impossible to meet a predetermined product release schedule.

Flow, from a quality documentation perspective, relative to the value stream discussed means that revision of controlled documentation is quick,

complete, controlled, and accurate with minimal wait times. Many employee frustrations in the value stream result from delays in document issuance, errors in issued documents that require further corrections, incomplete or partial revisions that require an additional document revision, excessive revisions per year, and wait times for required reviews and signatures.

Flow, from a discrepancy and failure investigation perspective, relative to the value stream discussed means that all the required investigation tools and information are available as needed. It also means that the investigation report is accurate, complete, thorough, consistent, and closes quickly, preferably prior to completion of the product manufacturing cycle. Many employee frustrations in the value stream result from delayed notification of the deviation, poor or no training on investigation tools and techniques, inability to obtain the required investigation information (trend reports, testing results, etc), increases in inventory (open deviation reports) due to closure delays, and high pressure to rush a report closure for batch release.

Flow, from a change control perspective, relative to the value stream discussed means that the validation is completed quickly, thoroughly, and properly. It also means that the required signers are involved, informed, and available (including regulatory affairs), assessments are correct, all required submissions and notifications are completed (regulatory affairs, customers, other facilities, etc), documents are issued, all plans are in place, and that all the required activities are executed concurrently when possible. Many employee

frustrations in the value stream (and outside the value stream) result from poor planning, poor organization, inadequate coordination, and delays in any or all of the sub-value streams required activities. These delays result in slow implementation of changes or improvements, increased costs, and increases in potential compliance and business risks.

Flow, from a validation perspective, relative to the value stream discussed means that the validation plan is thorough and complete. It also means that the required materials, employee resources, and space are available as needed, as well as completed on schedule. Many employee frustrations in the value stream (and outside the value steam) result from poor planning, poor organization, inadequate coordination, unavailability of required resources, lack of clarity of purchasing lead times, and delays in implementation of the equipment.

The primary causes for poor flow in the quality systems components value streams, which result in delays, wait times, and increased costs, are poor planning, poor understanding of requirements, poor understanding of expectations and consequences, ineffective organization, and failure to initiate the required activities immediately. All of the activities require a clear understanding of the regulations, requirements, existing procedures, and their interaction, in order to minimize delays in completion.

Pull

Pull refers to the concept that a good or service should not be produced (upstream) until the customer (downstream) asks for it. This may be the most

difficult principle to apply and realize. It is especially difficult to apply in a non-production setting. This is the batch-and-queue equivalent of just-in-time (JIT) thinking. Unfortunately, JIT has been applied mostly to the supply side for support of manufacturing activities, instead of the production side output to the customer (i.e. make the product when the customer asks for it). However, pull can have a radical impact on inventory reduction. Inventory reduction impacts money flow, as well as providing the customer the desired product, instead of what is available in inventory. Converting from departments and batches to product teams and flow dramatically reduces the cycle time of the product from raw materials to a product in the hands of the consumer. This includes design time (concept to launch), manufacture, and sale to delivery. An actual lean system can make any product currently in production in any combination, thereby reducing response time to changing demands, reducing wasted inventory (old inventory no longer wanted by the customer), and improving planning and predictability. This all results in the customer pulling the product as needed rather than pushing often unwanted product to the customer. Demand stabilizes because the customer knows they can get the product they want, when they want it (Womack, Lean Thinking, 2003).

With the FDA defined as the customer and the product defined as the deliverables required of the quality systems, the concept of pull, which is considered difficult in a manufacturing environment, becomes extremely difficult in a non-manufacturing environment. The primary application of pull for the

purposes of this paper focuses on inventory. Inventory consists of open or incomplete products (batch records, investigations, change requests, validations, etc.) that impact the manufacturing product cycle time, improvement time, and present potential compliance risks. The FDA expects that documentation be provided upon request; therefore, pull from the customer is not applicable, as the customer has been defined. However, the concept of pull can be applied to the quality systems components pulling the required information from the manufacturing cells. As related to manufacturing, this would be equivalent to pull on the supply side, which, along with inventory reduction, has been the most effective results of pull. The quality systems components value stream steps discussed in the value stream section are now examined.

Pull, from the batch release perspective, relative to the value stream discussed focuses on open batch records for manufactured product (inventory) and a supply side pull consisting of effective acquisition of required documentation from all areas. Open batch records represent inventory as a quality systems deliverable perspective, but also represent inventory from a manufactured product perspective. This presents a quality and business risk. Products or intermediates cannot be shipped until the batch record is reviewed, approved, and closed. Batch records remain open until all required information is obtained and acceptable. Pulling the required information from manufacturing, quality operations (approved manufacturing run sheets for buffers, reagents, and product), quality systems components (discrepancy and failure investigations,

change control, laboratory operations including raw materials approval and release, testing in chemistry, immunology, and microbiology – bacteriology of water and compressed gas systems – environmental monitoring of controlled areas, and sample control - accounting for all required samples and their conditions), and critical systems is the goal.

Pull, from the quality documentation perspective, relative to the value stream discussed focuses on open documentation change requests (inventory). Open documentation change requests represent inventory from a quality systems deliverable perspective. This is important because if a document is under change, no other changes can be made to the document until the first change is processed. Otherwise, there would be no control of the document and the associated required training. Also, sometimes changes must be made to documents as part of a corrective action resulting from a deviation investigation report related to the manufacturing process. Batch release requires closure of the document change prior to closure of the batch file, thereby impacting manufactured product release. Finally, any proposed change cannot be implemented until there is an effective date for the issuance of the document, even if training has already occurred through a training copy (not yet issued for official use). Therefore, it is important to close documentation change requests quickly.

Pull, from the discrepancy and failure investigation perspective, relative to the value stream discussed focuses on open discrepancy investigations

(inventory) and a supply side pull of required information from all areas contributing to the investigation. Open discrepancy investigations represent inventory as a quality systems deliverable perspective, but also represent inventory from a manufactured product perspective. Open discrepancy investigations represent enormous quality and business risks. Open investigations have not determined product impact, have not implemented any corrections or corrective actions, and have not evaluated upstream and downstream impact on product, equipment, or systems. Open product related investigations also hold open batch record files, thereby stopping the shipment of product and increasing manufactured product inventory.

Pull, from the change control perspective, relative to the value stream discussed would focus on open change requests (inventory) and a supply side pull of required information from all areas contributing to the completion of requirements as identified. Open change requests represent enormous quality and business risks. This inventory represents high compliance risks as well. The introduction of new equipment and processes that interact with existing systems and processes are difficult to isolate. There is potential negative impact to existing systems and processes, potential that the new equipment and process will be used inadvertently prior to authorization, and potential of validation personnel contaminating or interfering with the on-going product manufacturing activities. Although the change owner of the change request is responsible for completion of the requirements, change control will frequently have to provide

additional follow-up (pull), along with appropriate management to drive the change request to closure. Additionally, the new equipment and processes cannot be implemented until completion of the requirements and acquisition of the required approvals; therefore, the proposed improvements cannot be realized to improve the bottom line.

Pull, from the validation perspective, relative to the value stream discussed focuses on open validations (inventory) and a supply side pull of required information from all areas contributing to the completion of requirements as identified in the validation plan and protocol. Open validations represent enormous quality and business risks. Since validations are a subcomponent of the change request referenced above, the same information would apply here.

The primary causes for ineffective pull in the quality systems components value streams, which result in delays, wait times, and increased costs, are poor planning, ineffective organization, and failure to inform all parties involved of the needs, impact, and importance of the required activities. All of the activities require a clear understanding of the regulations, requirements, existing procedures, and their interaction, in order to minimize delays in completion.

Perfection

The fifth and final principle of Lean Thinking is perfection. Perfection is the complete elimination of muda. As the lean organizational culture develops, employee knowledge base and understanding of lean increases, and value begins to be more accurately specified. The value stream identity improves, the

value-added steps of specific products flow more continuously, and the customers are able to pull from the enterprise, and people (all employees) begin to realize there is no end to the improvements. The improvements result in reducing effort, time, space, cost, and mistakes while producing a product that comes closer and closer to meeting what the customer desires. At this point, perfection seems to become achievable. The first four principles interact by making value flow faster, which results in identification of hidden waste in the value stream. The more the customer pulls on the system, the more impediments to flow are identified and removed, driving continuous improvement. Dedicated product teams in direct dialogue with the customer, produce improved specification of value, flow, and pull. A truly lean enterprise that has effectively implemented transparency (information for everyone in real time) makes it easier to discover better ways to create value. Transparency in everything is a key sub-principle. This also results in instant and positive feedback for employees making improvements. As Womack and Jones state “Perfection is like infinity. Trying to envision it (and to get there) is actually impossible, but the effort to do so provides inspiration and direction essential to making progress along the path” (p. 94). In the beginning, it is very important for the perfection vision to select the two or three most important steps and not try to address perfection everywhere with insufficient resources. A picture of perfection requires a clear sense of direction. It also requires the knowledge that products must be manufactured

more flexibly, in smaller volumes, in continuous flow, and with a design that is easy to produce or manufacture (Womack, Lean Thinking, 2003).

Perfection in this application would result in all of the FDA required deliverables being closed prior to the end of the physical manufacturing cycle, resulting in the physical manufacturing cycle time being equal to the total product cycle time.

Key concepts applicable to pharmaceutical quality systems, defining the FDA as the customer and the required FDA deliverables as the product are: increases in employee knowledge and understanding, focus on customer value as defined by the customer, focus on the identified and mapped value streams, creating flow, muda elimination, inventory reduction and supply side pull, and transparency relative to information, projects, goals, performance measures, and plans. Each of the quality systems components identified represents a dedicated product team. Regulatory affairs and change control, as well as the current quality approved SOPs, provide direct dialogue with the customer to continually improve specification of value.

Additional Lean Information

Lean Thinking only flourishes if everyone along the value-stream, including senior management and the CEO, believes the new system being created treats everyone fairly and ensures support of human dilemmas. Otherwise, active sabotage will occur from within. A brief view of Lean Thinking

on the financials is provided, along with a brief discussion of the required steps to implement lean thinking across an organization from beginning to end.

From a financial perspective, Lean Thinking (manufacturing) provides three key improvements, increased capacity, increased space, and increased cash flow resulting from a reduction in inventory. It is critical to develop a plan to effectively utilize the increased availability of these resources to gain the maximum benefit. A lean accounting system is critical for measurement and providing information for decision-making. Cost systems provide two key measures. First, they value inventory; second, they provide information to manage and control operations. Standard cost accounting was designed to support mass production. Under Lean Thinking, the financial statements will show declining profits because the improvements have removed inventory available to absorb overhead allocations. The only benefit standard cost accounting provides under lean operations is valuation of inventory, which is greatly reduced but still very important to measure. Under Lean Thinking, the focus becomes optimizing the value-stream for a product family, not optimizing individual operations. The focus moves away from the least cost per unit at each operation to a focus on the least total cost of units shipped from the value-stream. A value-stream accounting system focuses on cell performance measures, value-stream performance measures, a value-stream profit-and-loss statement, improvements in capacity for decision-making, and provides a value-stream box score that integrates operational, capacity, and financial data. A

value-stream accounting system is fast enough to provide daily performance information for making operational and improvement decisions (Lean Enterprise Institute, article posted 6/25/03).

The key to implementation of Lean Thinking in the first six months is to find the right leaders (change agent) with the right knowledge. One should begin with a value stream in crisis (lever) or performing poorly that can quickly show improvement with little or no cash investment, educate everyone from the CEO to entry-level employees on Lean Thinking, identify and map the value streams, demonstrate radical improvement of an activity to eliminate muda (kaikaku), and expand the implementation scope to other areas or value streams. It is very important to generate an effective and practical strategy to fully utilize all of the resources made available (cash flow from inventory, increased capacity, increased space). From six months through the second year a new organization is created. This consists of reorganization by product line and identification of all primary and secondary value streams. A Lean Thinking function needs to be created to drive the process with allocated space and a list of implementation activities for incoming support personnel freed-up. Two of the most critical items in the implementation of Lean Thinking are to develop a growth plan, along with a plan to deal with excess people. Personnel who do not support, go along with, or give the new paradigm a chance must be removed quickly. A perfection mind set should be introduced by reevaluating the already improved process as soon as the initial improvement is complete, showing continuous improvement. One

should spread the transformation beyond the manufacturing floor. From the beginning of year three through the end of year four new business systems are put into place. One should introduce the lean accounting system discussed above, relate employee pay to firm performance, implement transparency including indicator and performance scoreboards, initiate policy deployment, and right size the tools to fit the new processes. The fifth year completes the transformation by extending the Lean Thinking processes and techniques to suppliers and customers. One should develop a lean global strategy and convert from a top-down driven improvement process to a bottom-up driven process (Womack, Lean Thinking, 2003). Most important is to remember that the implementation of Lean Thinking to pharmaceutical manufactures requires a strong change control process with a close working relationship to the lean function. All changes, improvements (changes), and modifications (changes) need to be evaluated for their impact to the current state of validation, current license requirements, submissions to regulatory authorities, submissions to customers, current regulations, and existing documentation. This includes obtaining the associated evaluation and approvals prior to implementation.

CHAPTER 4

RESULTS and DISCUSSIONS

The research and analysis clearly indicates that Lean Thinking manufacturing processes and techniques extrapolate well to pharmaceutical quality systems, defining the FDA as the customer, and the product as the FDA required deliverables. The results and discussions focus on the evaluation and clear identification of the customer and the product when implementing Lean Thinking to non-manufacturing systems. Next, an analysis of the five key principles of Lean Thinking relative to the FDA and the pharmaceutical industry are covered. Next, a discussion of the FDA along with other regulatory agencies systems based approach to inspections is discussed relative to Lean Thinking. Finally, additional benefits of reduced manufactured product cycle time and improved bottom line profit are discussed as a result of applying Lean Thinking to pharmaceutical quality systems.

In the application of Lean Thinking to non-manufacturing environments, the most critical elements are to clearly and specifically identify the customer and the associated product of the function being addressed. Within an organization there may be multiple combinations of customers, partners, and identified product lines depending on the system under discussion. This is the critical first step in the application of the Lean Thinking processes and techniques. For example, in pharmaceutical production, manufacturing may define its customer

as the consumer of the physically manufactured product, the physician prescribing the pharmaceutical product, or the hospital prescribing the pharmaceutical product. Manufacturing's partners would then be defined as all the support groups required to bring the product into the hands of the customer, such as quality systems, maintenance, engineering, shipping, etc. Beyond the manufacturing floor, the customer, partners, and product lines may be different. The engineering department may define its customer as manufacturing and the product as the introduction of new or modified validated equipment and manufacturing processes. The engineering department partners would be quality systems, regulatory affairs, and other support groups required to bring the product into the hands of the customer. The same pharmaceutical facility's quality systems customer may be defined as the FDA and other regulatory agencies (for global distribution) since the manufacture, packaging, labeling, and distribution of pharmaceutical products is contingent upon consent and approval of the regulatory authorities. The product may be defined as the FDA and other regulatory agencies' required deliverables. The quality systems' partners would then be defined as all the other support groups, including manufacturing required to bring the product (FDA required deliverables) into the hands of the customer (FDA). It is critical that customer value frequently be reviewed and revised as necessary to consistently satisfy the customer over time and maintain focus on the customer. After a thorough evaluation of the pharmaceutical industry's quality system requirements, the research and analysis performed here defined the

customer of a pharmaceutical manufacturer's quality systems as the FDA, and the product is defined as the FDA required deliverables.

Lean Thinking provides an efficient and effective process for specifying value as defined by the FDA (customer), and identifying and mapping the value stream of each product line (quality data and information deliverables required by FDA). It includes making the value-creating steps flow and pulling the required information from the manufacturing process and support systems (supply side pull from quality operations and the manufacturing product cell), and finally, achieving perfection of the process through continuous improvement and the complete elimination of muda. Efficiency of product flow and effectiveness of the process to produce the customer defined and desired product is critical. The FDA defines value according to the documents listed in the value section. A summary of the all the quality systems components, along with their requirements to ensure compliance, is also included in the value section. The product lines or value streams are all FDA required deliverables produced by the quality systems for the customer. Quality systems components, batch release, quality documentation, discrepancy and failure investigations, change control, and validations had their value streams identified, with one value stream detailed to the activity level in the value stream section. The same quality systems components were evaluated for flow, pull, and perfection as well. Quality systems flow results in providing consistency of FDA deliverables across multiple manufacturing cells in a timely manner. Flow, relative to the quality systems

products means that the FDA required deliverables flow unimpeded to completion or closure, without wait times, backflows, backlogs, modifications or recreation of data or information. This requires an intimate interaction and communication with all initiators, generators or creators of FDA deliverables to ensure that the required information is produced, in the proper form, at all points in the process. This includes the purchase of raw materials, the manufacturing cycle, final product testing, sterilization, packaging, labeling, and shipping. Pull is a difficult concept to achieve in manufacturing, where it originated, and is exceptionally difficult to achieve in a non-manufacturing application. As in manufacturing, pull from a quality systems perspective is most effective on the supply side. The supply side consists of the initiators, generators or creators of the FDA required deliverables. The second focus of pull is on inventory reduction, as in manufacturing. Inventory consists of all the information and reports required by the FDA. The longer the information or report is incomplete, the longer the total manufacturing cycle time. Therefore, inventory relative to the quality systems products directly relates to inventory in the manufactured product as well. This creates business risks and quality risks. Perfection in this application would result in all of the FDA required deliverables being closed prior to the end of the physical manufacturing. This results in the physical manufacturing and testing cycle time being equal to the total product cycle time. It is important to keep in mind that approximately two-thirds of the total manufacturing cycle is post manufacturing. This means that only one-third of the time required to get the

manufactured product into the hands of the customer is the manufacturing process.

The federal government and the FDA provide extensive documentation concerning the laws, regulations, and compliance expectations relative to pharmaceutical manufacturing for protection of the consumer. This represents value as defined by the customer. It also has extensive enforcement capabilities available for non-compliance or failure to have adequate and effective systems in place to address the required regulations. Compliance costs are far less than non-compliance costs. The CPGMs provide an excellent, understandable FDA interpretation of the regulations. It is important to keep in mind that the use of the CPGMs does not eliminate the need to understand the details of the actual regulations. The FDA utilizes a systems based inspection for drug and biologic product manufacturers, as well as for medical devices (Quality Systems Inspection Technique (QSIT)). The European Union (EU) also utilizes a systems based inspection approach for verification of compliance (Quality Systems Requirements (QSRs)). The International Standards Organization (ISO) also utilizes a systems based inspection approach (see Washington Business Information--The Food and Drug Letter, 12/21/1; Washington Drug Letter, 3/19/04; Drug GMP Report, March 2004; Washington Drug Letter, 9/3/01). Per CPGM, 7356.002, focusing on systems, rather than individual product lines, will increase efficiency in conducting inspections because the systems are applicable to multiple product lines. The global trend is toward systems based inspections

for efficiency, effectiveness, and cost reduction. Therefore, organization of the quality systems as systems that cover multiple product lines benefits the FDA, other regulatory agencies, and the organization. The systems based approach for quality systems fits very well with Lean Thinking, which is a customer focused and product line (or product system) based manufacturing approach. Lean Thinking is a proven manufacturing technique that results in increases in output through increases in capacity, reductions in cost through elimination of waste, reductions in inventory and space, and continuous improvement in the process and quality of the product. The pharmaceutical manufacturer may produce multiple product lines at the same facility with a lean cellular organization. However, the quality systems components need to be centralized and consistent across all product lines, which puts the quality systems in alignment with the FDA inspection approach and requirements. The centralized quality systems components may have personnel dedicated to each manufacturing product line, but the personnel would report to the quality systems component manager or leader. As with Lean Thinking, the personnel should be cross trained to understand all manufactured product lines, but an intimate understanding of a product line only comes with time in a specific value stream, which also improves efficiency of activities. This central reporting is critical to ensure that the interpretation of the quality systems components SOPs are consistent across all manufacturing product lines. It also provides an assigned person for interaction with the FDA during the system based inspections. The FDA inspects systems,

not individual product lines. This organizational structure should minimize inspection time, maximize compliance, minimize inspection findings, minimize inconsistencies, and make any quality systems changes easier to implement across the multiple manufacturing product lines. Additionally, many quality systems activities require specialized training for personnel to be effective. The most important consideration in the organizational structure is that each quality system component cover all manufactured product lines. The name and number of the quality systems components is not important, as long as the requirements in every component identified in the value section are covered. The value streams within each quality system component may vary from corporation to corporation. The presented value streams were grouped under a specific quality systems component based on similarity or overlap of activities and required skill sets. However, the identified quality systems components' names and associated product lines are directly aligned with the FDA inspection approach. They ensure that all required information has an assigned responsibility and that the information is collected, complete, organized, and available when requested.

Although the primary focus has been on efficient, effective compliance, there are additional valuable results of the proposed structure and Lean Thinking approach to quality systems. There are benefits to manufacturing cycle time and bottom line profit. Approximately two-thirds of the total manufacturing product cycle time is post-manufacturing (time not spent working on the actual product). This information will be revealed during the manufacturing value stream mapping

process and will be available after the manufacturing operations have transformed to Lean Thinking. Most of the post-manufacturing time consists of closing deviation investigations, laboratory test failure investigations, environmental monitoring failure investigations, change control file closures, validation closures, other report closures, and corrections of the good documentations practices deviations. After Lean Thinking is applied, the quality systems components value and the associated value streams will be clearly defined and mapped, exhibiting flow (elimination of wait time), and executing supply side pull of the required manufacturing and quality operations information. Quality systems products (investigations, change request, etc) will also experience an inventory reduction (fewer open files and quicker closure of files) resulting from focus and the pull principle. The result of all of this will be a reduction of post manufacturing time, a reduction in manufactured product inventory waiting for release, an increase in total manufacturing product output capacity, and the associated increase in bottom line profit. There should also be a reduction in total quality systems personnel, employee turnover, and an associated increase in space as a result of the implementation of Lean Thinking in the quality systems.

CHAPTER 5

SUMMARY, CONCLUSIONS, AND RECOMMENDATIONS

The FDA is a U.S. government agency that has been charged with the protection of public health by assuring the identity, strength, quality, effectiveness, safety, and purity of the drugs, biologics, and medical devices. The FDA is responsible for advancing the public health by helping speed innovations that make medicines more effective, safer, and more affordable. The FDA is also responsible for helping the public get the accurate, science-based information they need to use medicines to improve their health. The FDA receives its powers from the FD&C. The FDA has significant monitoring and enforcement powers covering the design, development, storage, manufacturing, testing, labeling, documentation, distribution, import, performance claims, advertisement, and use of drugs, biologics, and medical devices. The FDA must approve a drug for marketing before it is made commercially available to the public. The FDA oversees items accounting for 25 cents of every dollar spent by consumers and has oversite responsibility for the sale of about $1 trillion worth of products annually that cost taxpayers about $3 per person. The agency grew from a single chemist in 1892 to over 9,000 employees and a budget of $1.3 billion in 2001 (Food and Drug). Today drug consumers trustingly take prescription and non-prescription drugs knowing that the FDA ensures the identity, strength, quality, effectiveness, and purity of the drug.

The FDA moved from a product based inspection approach to a systems based inspection approach in February of 2002 for drug inspections. Medical devices moved to a systems based inspection approach in the mid 1990s. Compliance with FDA regulations in the manufacture of drugs, drug products, and biologics is extremely expensive in the highly competitive pharmaceutical industry. Non-compliance is even more expensive. Quality systems are required to ensure, verify, and document that the company maintains compliance to cGMPs, governing regulations, internal procedures, specifications, and to ensure adequate systems exist to prevent and resolve difficulties during manufacturing. All these activities result in extremely high overhead costs (millions of dollars in staff and documentation), and these costs must be controlled and minimized.

Lean Thinking is a combination of the best processes and practices that optimize resources and yield the best product, in the fastest time, at the lowest cost. Lean is an umbrella for “total quality management,” “continuous improvement, “zero defect,” “six sigma,” “DMAIC,” and other similar terms that focus on doing the right thing, at the right time, in the right place, in the right quantity, and doing it right the first time. Lean is significantly different from traditional, internally focused, push production concepts and approaches of batch-and-queue manufacturing, with high inventory, long wait times, high backflow and value defined by the corporation. Lean manufacturing focuses on single-piece flow, defining value from the customers view, elimination of muda, minimal inventory, using worker capabilities, fast cycle time, and cellular

organization by product lines or product teams (product systems). One of the first flow thinkers was Henry Ford, with dedicated tools and the beginnings of integrated product development. Taiichi Ohno of Toyota in Japan developed many techniques for automotive production facilities that are still the key focus of Lean Thinking today. He focused on:

- Set-up time reductions,
- Simplification of activities,
- Making a few parts; instead, of huge inventories,
- Quick identification of errors,
- Reducing the number of bad parts manufactured,
- Allowing every employee could stop the production line when a problem occurred,
- Ensuring a highly skilled and motivated work force,
- Reducing muda,
- Establishing work teams with full responsibility for housekeeping, minor tool repair, quality checking and incremental or small improvements through collective thinking (kaizen) for a portion of the process,
- Instituting a problem solving system called “the five why’s” to ensure the root cause was identified and eliminated permanently,
- Offering lifetime employment,
- Pay by seniority, instead of job function, tied to profitability through bonuses,

- Rewards and advancement for team players,
- Employees' commitment to flexibility in work assignments and initiating improvements, instead of just responding to problems (Deming's idea of "cooperation"),
- Consulting directly with existing customers in planning new products.

These actions and others resulted in nearly 100% yield and a drastic drop in rework and waste (Womack, Lean Thinking, 2003). These same techniques were applied to suppliers (partners) so that everyone benefited (win-win). As with most drastic changes in corporate focus and operations, the Chief Executive Officer (CEO) must support the lean approach. These concepts and techniques have been applied in many other manufacturing operations with great success. They have also been applied to a few non-manufacturing operations with great success.

This paper examined the application of Lean Thinking to pharmaceutical quality systems, defining the FDA as the customer. The product is defined as the deliverables required by the FDA. Lean Thinking provides an effective and efficient process for specifying value as defined by the FDA, and identifying and mapping the value streams (activities to generated the FDA required deliverables). It also includes making the value-creating steps flow and pulling the required information from the manufacturing process and quality operations (supply side pull with deliverables inventory reductions), and finally, achieving perfection of process.

Lean Thinking can be summarized in five key principles designed to eliminate muda:

- Precisely specify “value” by specific product,
- Identify the “value stream” for each product,
- Make the value “flow” without interruptions,
- Let the customer “pull” value from the producer,
- Pursue “perfection.”

The meta-principle of Lean Thinking is responsiveness to change and waste minimization (Womack, Lean Thinking, 2003).

Value as defined by the FDA for drugs is contained in five types of documents utilized by the FDA to ensure the manufacturer’s products are safe, effective, have the identity and strength, and meet the quality and purity characteristics as intended: FD&C, 21 CFR and Federal Register, Compliance Program Guidance Manuals (CPGM), other manuals, and Human Drug cGMP Notes issued by the FDA, for the FDA and industry. All referenced documents are available on the FDA website.

The key quality systems components identified to ensure compliance as defined by the above referenced documents are:

- Batch Release,
- Quality Documentation,
- Discrepancy and Failure Investigations,

- Stability Failure Investigations with Field Alert Evaluations,
- Corrective Actions and Preventative Actions (CAPAs),
- Complaint Reviews (quality and medical),
- Rejects and Returns and Salvages Assessment, Investigation, and Disposition,
- Change Control,
- Validations,
- Material Qualification,
- Laboratory Operations,
- Metrology,
- Raw Material Receiving and Release,
- Sample Control,
- Training and Qualification of Employees,
- Supplier Quality Approval and Contracts,
- Quality Auditing (internal, external),
- Annual Record Review,
- Management Review of the Quality System,
- Quality Operations.

Some of the quality systems components may be grouped together as demonstrated in the value section. Each corporation may have it's own approach

on how to group the required components. Primary and secondary value streams exist within each quality systems components. This research took five quality systems components identified in the value section and carried the Lean Thinking extrapolation and application process through value streams, flow, pull, and perfection. The five quality system components are batch release, quality documentation, discrepancy and failure investigations, change control, and validations. Each component had the requisite value streams identified with one of value streams activities detailed. No actual value stream mapping was performed in the research.

Variation exists in all processes and systems. Continuous focus on variation reduction is critical to any improvement activities (special and common). Root cause analysis and other quality improvement tools (six sigma, DMAIC, SPC, etc.) are critical tools used in conjunction with Lean Thinking. Their use will assist in the elimination or reduction of the common cause variation, which results in a tighter (smaller standard deviation), more stable (predictable) process.

Key concepts applicable to pharmaceutical quality systems, defining the FDA as the customer and the required deliverables as the product are: increases in employee knowledge and understanding, focus on customer value as defined by the customer, focus on the identified and mapped value streams, creating flow, waste elimination, inventory reduction and supply side pull, and transparency relative to information, projects, goals, performance measures, and

plans. Each of the quality systems components identified represents a dedicated product team. Regulatory affairs and change control, as well as the current quality approved SOPs, provide direct dialogue with the FDA to continually improve the specification of value.

The Lean Thinking manufacturing approach extrapolates well to pharmaceutical quality systems when the FDA is defined as the customer and the product line is defined as the FDA required deliverables. Organizing the quality systems components as identified in this research should produce an efficient, effective, and compliant pharmaceutical manufacturing facility that excels in a highly competitive industry.

The limitations and weakness of the study are that every quality systems component was not carried through the entire process. Batch release, quality documentation, discrepancy and failure investigations, change control, and validations had their associated value streams identified but only one of the value streams was detailed by activities. Stability failure investigations with field alert evaluations, corrective actions and preventative actions (CAPAs), complaint reviews (quality and medical), rejects and returns (salvages assessment, investigation, and disposition), material qualification, laboratory operations, metrology, raw material receiving and release, sample control, training and qualification of employees, supplier quality approval and contracts, quality auditing (internal, external), annual record review, management review of the quality system, and quality operations did not have their value streams identified

and were not carried through the entire Lean Thinking process, although an overview of their responsibilities as derived from the FDA documents was presented in the value section. Another limitation or weakness of the study is the absence of actual value stream mapping. Finally, there was no opportunity to implement the actual organization identified and carry the entire process to its final end.

Implications for future research would consist of completing any or all the limitations and weaknesses identified above and most importantly, implementing the concept. I hope to implement this approach in the near future.

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