**Process-Health(care) in Clinical Research**

Enhancing Regulatory Compliance with Lean Six Sigma ‘Thinking’

***“Everything should be made as simple as possible, but not one bit simpler.”***- Albert Einstein

**Current State**

The medical drug and device research industry is no different than any other field. In the simplest of terms, it’s about knowing customer needs better than competitors, designing products easier, soliciting regulatory approval faster and reproducing market delight cheaper.

On average, it takes 10 years to bring a new drug from concept to market. The last blockbuster drugs were approved in 2006. Although companies worldwide are clamoring for the next miracle, the price tag to bring a new drug to market is estimated between US$1.3 and US$1.7 billion dollars.1 When the bulk of these finances are spent conducting the clinical study trials, and regulatory approval to market the investigational product (IP) occurs only after these trials, concerted effort to reduce wasted time, money, and resources of a clinical trial is paramount. Biopharmaceutical and device industries have long recognized the need to decrease development time and bring more investigational products (IP) to market faster. Current methods of bringing IP to market have to change.

Waste, which can be defined as process steps that do not add value for the customer, occurs in various forms and at all levels in the clinical study trial. The collection of extraneous data on case report forms is a prime example of waste. “Sponsors estimate that 15% to as much as 30% of all clinical data collected is not used in NDA [New Drug Application] submissions. For an average drug, streamlining the collection of data to limit and even remove the incidence of unused data represents approximately $20 to $35 million in direct drug development cost savings.”2 Conducting sponsor or government regulatory audits at the close of a study or in response to a NDA or device pre-market approval (PMA) submissions forfeits the opportunity to identify and correct problems with the data or the manner in which it was obtained. Regretfully, there is currently no way to ‘inspect in’ quality; this manner of auditing wastes resources and time. When communication of information and ideas is isolated or ‘siloed’ within company departments, or regulatory approval for an IP that will be marketed globally is obtained on an individual basis by each governing agency as opposed to a joint approval, waste has occurred.

Recently though, regulatory agencies worldwide have started to appreciate the benefit of reciprocal Good Clinical Practices (GCPs). They have commenced partnerships to identify the similarities and differences in their laws and regulations to encourage more studies from more countries and to use clinical data to facilitate regulatory submissions respectively. One such collaboration is the Harmonize-by-Doing program between the FDA and the Japanese Ministry of Health, Welfare, and Labor to enable advancements with device medical research for both countries. According to Neal Fearnot, VP of Cook Group Incorporated and a member of the Harmonize-by-Doing Working Group 4, “Recognition of inefficient practices and unnecessary efforts provides an opportunity to define best practices that will improve the quality and reduce the cost of clinical studies and regulatory approvals in both countries, thereby lowering the costs of product development and the devices themselves.”3 Additionally, the FDA has collaborated with the EMA and “in order to use resources more efficiently…[they] have launched a pilot program to share information on drug applications and GCP inspections, with an eye to relying more on each other’s inspection findings and to avoid duplicative efforts.”4

These government initiatives demonstrate collaboration (teamwork), process improvement by identifying process flow and inefficient practices (or variation and defects), as well as, improving overall quality and speed; all of which are based on data and facts. These principles that are valued by the regulatory agencies (a customer to sponsors) comprise Lean Six Sigma (LSS) thinking.

**Hybrid Improvement**
Remember over the years ‘process improvement’ efforts have changed. From Henry Ford’s centralized production, to the Shewart/Deming PDCA Cycle, to Toyota’s Production System, on through to today’s Lean Six Sigma (LSS) successful companies have done a good job of building on prior methodologies. LSS brings together various approaches from the past which were often applied in a vacuum. The strength of LSS is the ’system’ approach, rather than ’process’ approach. Few companies today apply the strict traditional Total Quality Management (TQM) approach alone, yet no one would say ‘quality’ isn’t important, rather quality is one piece, one facet of enterprise management.

To continue, let’s get the traditional definition of each of our subjects out of the way. "Lean Manufacturing", often referred to as just "lean," is a production strategy. It considers the exploitation of resources and/or materials for any goal other than the creation of customer-perceived value as wasteful, and targeted for elimination. At its core, lean drives value while maintaining excellence.

"Six Sigma," is a mathematical calculation tied to the standard deviation’s distance from a data distribution mean. It seeks to improve the quality of outputs by identifying/removing the cause of errors and variability. It combines quality management methods, statistics, and assigns competence levels to its practitioners within an organization ("Black Belts", "Green Belts", etc.).

In the past many companies had both lean experts and six sigma black belts, who often reported along different lines of communication chains of command. In the industries we work in we saw this approach divided resources, created unnecessary competition, and split camps. Other successful companies, too, began to combine the two approaches into one methodology. Thus the application of Lean Six Sigma was born.

**Applying the ‘System’**
For years we had the privilege of working alongside some of Toyota’s former leaders, who had transferred to the consulting business. We would travel the country together spending weeks with plant managers and floor-level workers. We would ask the hard questions, we would encourage successes and point out the opportunities for improvement. Along the way in observing their approach, we began to see that most organizations that attempted to adopt ‘lean’ did it by narrowly applying the philosophy. It really turned into learning a new tool exercise as opposed to sustainable culture growth. In fact, even today many companies only see Lean Six Sigma (LSS) as a set of tools and have limited spotty improvement, and wonder why.

We shouldn’t kid ourselves. The goal of LSS is to save and/or make more money, period. Only when it is viewed properly, as a ‘system’ will it take clear effect. Certainly when applied correctly you will use ‘tools,’ but if the foundational thinking is forgotten or never learned, it will fall by the wayside as the latest management fad. So what is this foundational LSS thinking specifically? Since earlier we spoke of money, let’s take a closer look at that.

**An Illustration**
Most would report that there are two sides to a coin, yet if the edge is considered would there be three sides? The design of a coin is a simple way to remember core values of LSS.

*Taiichi Ohno is considered to be the father of the* ***Toyota Production System*** *which became* ***Lean Manufacturing*** *in the U.S.*



**LSS Thinking - Side 1: HONOR Standards!**Not necessarily writing, publishing, editing or distributing them, but honoring them. In the spirit on the first ISO 9001 mantra, "document what you do, do what you document, and prove it in practice." Standards are the only sustained foundation for improvement. Automotive entrepreneur, Henry Ford said, "today's standardization is the necessary foundation on which tomorrow's improvement will be based. “If you think of ‘standardization’ as the best you know today, but which is to be improved tomorrow, you get somewhere."5 And then later, Toyota Production System creator Taiichi Ohno reaffirmed that truth. "Where there is no Standard, there can be no Kaizen (improvement.)" So the first side of the LSS coin is to get serious about your written regulations, procedures and those pesky audits, for they are the foundation of stability.

**LSS Thinking - Side 2: HONOR People’s Good ideas!**People want to be in on things, they want to have a ‘say.’ Allow your workers to really contribute. Here’s the fun part. Workers are less skeptical of management when they know their business culture honors standards. In this environment, workers are more likely to give input, because they know if their opinions are right, backed by data, the organization’s culture is mature enough to implement their good ideas. This is a tremendous motivating factor. Collaboration and empowerment are true enablers for improvement and the second side of LSS.

**LSS Thinking - Side 3/Edge: HONOR the Customer!**The only side that connects both sides to a coin is the edge. As in the customer should be the central reason for all your standards and improvement efforts. They should touch all aspects of your business plan and execution.

**Investigational Product Value Stream**

A useful tool of LSS is the construction of a value stream. A value stream utilizes symbols to illustrate the sequential set of activities from bringing raw materials, or in the case of clinical research, the concept of the IP, to finished goods, or the IP to market following regulatory approval. This process allows team members to identify and visualize the steps currently used to bring a product to market. The value stream also aids to identify unnecessary processes, or waste, that does not add value to the investigational product from the perspective of the customer. Customers may be internal to the company, such as those staff members who are next in the sequence of steps toward marketing the device, or external, such as a regulatory agency who will grant IP approval for marketing.

Figure 1 provides an enterprise model of the investigational product value stream.

Figure 1



**High level process sequence in medical research:**
1. Capturing the need: *Agree on clinical trial with CRO/Pharmaceutical client.*
2. Bringing concept to life: *Begin and monitor the clinical trial process.*3. Approving the product: *Collaborate with approval agencies.* 4. Building the product: *Identify and eliminate waste.*
4. Selling to market: *Publish the results and transmit the data to client, CRO, etc.*

**Opportunity for Proven Results**
Critical truth: There is much more opportunity (‘starbursts’ on map) for competitive advantage in product development than anywhere else along the value stream (steps 2-3 above), as the following statistics show. Approximately 30% to 50% of the cost in service organizations is related to slow speed and performing rework to satisfy customer needs.6 With non-value added activities and waste for R&D upwards to 80% and in manufacturing up to 50%, many developers are looking for efficiencies. Below are just a few of the recent healthcare process breakthroughs.

**LSS in Medical Research**
-H. Lee Moffitt Cancer Center and Research Institute is expected to increase procedural volume by 12%, which will add nearly $8 million annually in incremental margin. – Tampa Bay Business Journal 7
-Omnex - In their clinical research patient recruitment cycle time reduced by 48%, rework reduced by 32%, cycle time improved by 41% and space and walking by nurses reduced by 28%. 8
-Dowpharma improved a yield from 40% to 87% by more tightly controlling two process variables and increased the capacity of a plant by a factor of 7.5 through an add-on investment, amounting to just 3% of the cost of the facility. 9

**LSS in General Healthcare**
-The Pittsburgh Regional Healthcare Initiative cut the amount of reported central line-associated bloodstream infections by more than 50%. The rate per 1,000 line days (the measure hospitals use) plummeted from 4.2 to 1.9. – ASQ.org (American Society for Quality)
-A top-five hospital system used Lean Six Sigma to redesign its transplant unit and as a result improved patient satisfaction by 50% within three months; the cost of care was reduced by 15%. – Quality Digest
-North Mississippi Medical Center reduced the number of prescription errors in discharge documents by 50%. – ASQ.org (American Society for Quality)

**Lessons Learned**

Obviously medical drug and/or device improvements revolve around two primary areas. For one, quality; in regards to Non-Conformances (NCs) and Corrective and Preventive Actions (CAPA) and secondly around regulatory partnership, management and the development and control of your standards, policies and procedures. Successful companies are planning for error-proofing their practices to ensure minimal negative governmental intervention. However when “warning letters” arrive, LSS-savvy managers know crises can be your teams’ best friend for harnessing focus. Let’s take a look at a half-dozen, recent real-life, “warning letters,” determine their root cause and suggest some LSS tools to prevent this from occurring again.

**Issue #1: Failure to ensure that the study was conducted to the signed investigator statement.**

***Root Cause:*** *Improper randomization and allowing multiple un-informed sub-investigators to perform the work.*

***Suggested Tool:*** *PDCA, the plan–do–check–act cycle is a four-step change model. Obviously if proper controls were put in place during the check phase such as un-announced internal audits, this could have been prevented. Cause and Effect Diagram to brainstorm and identify likely causes for the error followed by 5-Why’s to get to the root cause. Although this was a failure to detect the error at the end of the process the problem likely started, and thus could have been prevented, much earlier in the process*

**Issue #2: Failure to maintain adequate and accurate case histories that record observation and pertinent data.**

***Root Cause:*** *Workers were allowed to miss the required documentation.*

***Suggested Tool:*** *Error proofing, refers to the implementation of fail-safe mechanisms to prevent a process from producing defects. This activity is also know by the Japanese term poka-yoke, from poka (inadvertent errors) and yokeru (to avoid) - pronounced POH-kuh YOH-kay. A simple “no advance” template similar to filling out an online form may have prevented this.*

**Issue #3: Failure to obtain informed consent.**

***Root Cause:*** *Untrained employees*

***Suggested Tool:*** *Standardized Work Job Instructions (SWJI), not to be confused with Standard Operating Procedures. SWJI consist of a number of graphic, easy-to-follow, at the work site instructions that ensure consistency in the work being done. Help the employee see what “right” looks like, accelerates learning, and improves quality. Checklists, when properly used, can add consistency to a process, consistency improves quality and should supplement good management practices.*

**Issue #4: Failure to maintain adequate records regarding disposition of the IP.**

***Root Cause:*** *No organized standard for older data.*

***Suggested Tool:*** *5S, meaning Sort, Straighten, Shine, Standardize, and Sustain: a workplace discipline used to ensure reliable work practices and a clean working environment and can be applied readily to electronic filing systems as well*. *5S main purpose is to show an “out of standard” condition and is a foundation for the implementation of many other tools*

**Issue #5: Failure to report to the regulatory agency unanticipated problems involving human error.**

***Root Cause:*** *Rushing the process and taking shortcuts.*

***Suggested Tool:*** *FMEA, an analytical technique used by product or process designers as a means to ensure that, to the extent possible, potential failure modes and their associated causes have been considered and addressed prior to implementation. It’s best for the design to be based on the results of the FMEA study.*

**Issue #6: Failure to personally conduct the clinical investigation.**

***Root Cause:*** *Excessive delegation due to over-extended responsibilities*

***Suggested Tool:*** *GEMBA, is a Japanese term meaning go to/go see "the actual place." Responsible leaders and managers mustpractice thisso that they can see for themselves how the work is performed and what obstacles exist. The actual work doesn’t always follow the blueprint designed by the engineers. When you go to GEMBA you don’t need to assume because now you know.*

**Conclusion-Future State**

***"Improvement usually means doing something that we have never done before*.”** - Shigeo Shingo

The relationship between LSS ‘thinking’ and LSS ‘tools’ must never be separated. Based upon our experience both within research and outside the industry, here are four tangible suggestions for minimizing undue regulatory interference.
-Implement, publish and reinforce LSS design, process and employee skill-set standards. Hold all accountable.
-Educate all employees to see waste and unnecessary variability.
-Include upstream suppliers and downstream manufacturers early in the development discussion.
-Evaluate your system regularly for compliance issues and don’t be afraid of “fresh eyes” assistance.

We believe *STRUCTURE* drives *BEHAVIOR* which defines *CULTURE*.

Sponsors, CRO’s, and other medical practitioners directly involved in investigational drug and device development should take seriously the importance of utilizing standards as the foundation for improvement. Following the current policies and procedures provides a clear foundation, a measuring point to launch innovative ideas. If it can't be measured, it can't be improved. In review, honoring standards is more than understanding them-it's requiring their application with a vengeance. No exceptions! In essence, be autocratic about standards. It has been said, “Show me how I’m measured, and I’ll show you how I behave.” Managers should continually ask themselves, ‘are they providing clear expectations (metrics) and giving their people the opportunity to contribute in order to minimize risk?’ In essence be participative about people. Culture, on the other hand, is the fruit, the by-product, the effect or the result…of your practiced structure and your approved behaviors.

Managers desire a risk-aware culture whose people know the expectations of both customers and regulators alike. Proper foundational Lean Six Sigma ‘thinking’ can help them balance the two and ameliorate regulatory compliance. Efficiency and compliance are not mutually exclusive, rather two blades in a pair of scissors -- you must have both to cut waste.

**References:**

1. <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2630351/>. Accessed: 8/30/10
2. Getz, Kenneth A. Applied Clinical Trials. With Clinical Data, Less Is More. P. 28-30. January 2010
3. Neal Farnot, MED INSTITUTE, INC.
4. Wechsler, Jill. Applied Clinical Trials. *Clinical Trials Face New Enforcement Models*. p. 22-24. June 2010.
5. Henry Ford, Today and Tomorrow, 1926
6. Michael L. George, LSS for Service, McGraw-Hill, 2003
7. Margie Manning, Senior Writer-Efficiency paying off at Moffitt, St. Joe’s, Tampa Bay Business Journal,
 September 28, 2009
8. <http://www.omnex.com/healthcare/linked_articles/CS_1_Omnex_Process_Improvement_in_Clinical_Research.doc>
9. <http://www.genengnews.com/gen-articles/lean-and-six-sigma-approaches-taking-hold/1510/>

**Bio:**Timothy W. Fowler is a Continuous Improvement Manager currently serving in Afghanistan (2013) assisting NATO and the US Army with system improvement. His past efforts also include the Missile Defense Agency and other defense related departments including the POTUS secure refueling process with Air Force One.

He is a University of Kentucky Certified Lean Master, an Avraham Y. Goldratt Theory of Constraints Design Expert and an ASQ-Certified Six Sigma Black Belt. He was the first certified Lean Coach at the Ford Motor Company and was a Psychiatric Social Worker at numerous hospitals before working in manufacturing and defense. For assistance, he can be reached at timothyfowler@aol.com. His magicjack phone number is (216) 769-9713

 