

LEAN AND SIX SIGMA CONCEPTS APPLICATION IN PHARMACEUTICAL INDUSTRY

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LEAN thinking and Six Sigma have been utilized by manufacturing industries to decrease cost and improve quality and productivity by reducing variation and production defects [1]. Because of the dramatic successes in manufacturing, there is rising interest among companies in the pharmaceutical industry, which chooses to implement LEAN in order to accomplish such goals as decreased wait time to release product to the market, reduce production waste, and improve communication with end users and raise quality level both in the production and in testing laboratories. In this article, basics of LEAN and Six Sigma are presented and suggestion was given for application of their concepts in pharmaceutical industry together with harmonization with legal regulation represented by requirements Good Manufacturing Practice (cGMP), in order to work "smarter", more cost-effectively and avoid wasting time and other resources.

Keywords: Lean concept, Six Sigma, cGMP, pharmaceutical industry

1. CURRENT STATUS

Process improvement initiatives have been in existence for quite some time and include Continuous Quality Improvement (CQI), Process Improvement (PI), Quality Assurance (QA), Quality Management (QM) and Re-engineering. In the mid-1900s, the term Six sigma was coined by a Motorola Engineer, Bill Smith, to describe a new quality control process that merged from the Total Quality Management (TQM) strategy and was very successful in improving profits.

Six Sigma is a methodology of continuous improvement aimed at reducing defects by using the model Define-Measure-Analyze-Improve-Control (DMAIC), which is further developed through the Design for Six Sigma, which is based on creating a robust design that meets customer requirements and Lean Six Sigma, which is based on the processes and ways to increase their efficiency [2].

LEAN was founded by Taiichi Ohno in the 1950s and arose from the Toyota production System with key aspects including the never-ending quest for perfection, continuous search to eliminate waste and the recognition and importance of employee contributions [1].

Lean and Six Sigma as methodologies can be used independently or together. Today, many companies in different industries, both large and small, adopt Six Sigma and Lean as a regular way to improve the efficiency of design, manufacturing, business processes and intellectual property while reducing costs. Both concepts can be successfully applied in the pharmaceutical and medical device industry, in order to resolve the issue of unnecessary costs that limit profitable innovation.

Today pharmaceutical companies are faced with

demanding tasks such as adjustment to the unstable and turbulent market in times of economic crisis, as well as aiming to meet the needs of their users in maintaining their health. This specially comes to the fore in times of large number of new and untested infectious diseases such as swine flu, and its cause the virus H1N1. In order to meet all requests and requirements and respond to the challenges these companies are struggling to find ways to reduce internal costs and cycle times by providing high quality services to users, through innovative design and efficient response to the unexpected increase in demand for certain products.

However, balancing between the desire to reduce costs, on one side and innovative design, on the other is often very difficult. Thus, for example, when it comes to merging of pharmaceutical companies, the initial intention is to reduce costs, what in case of research and development (R & D) departments means a cut off [3]. Although there is still no right solution to these economic problems, the methods of Lean and Six Sigma can reduce costs, and encourage research and development, even in this time of great challenges.

Pharmaceutical and medical device manufacturers are looking in Lean manufacturing and Six sigma principles the way for significant improvement of operational efficiency and quality, while facilitating compliance.

Today, manufacturers in these industries are focused as never before on reducing operational costs while ensuring compliance. To ensure a solid position on the market and competitive advantage they are looking to increase the efficiency of their operational and manufacturing processes – optimizing resources, improving efficiency, reducing waste and controlling inventory [4].

The good news in this situation for companies in

pharmaceutical and medical device industry is that the initiatives of regulatory bodies (such as the FDA (Food and Drug Administration) and others) support these changes with the risk reduction approach as the embedding of quality in the manufacturing process from the very beginning (adopted principle known as quality by design - QbD) instead of relying on the final laboratory testing (adopted principle known as quality by testing - QbT). All previously presented elements and current developments in the pharmaceutical and medical device industry are in favor that it is now an ideal time to turn to the principles of Six Sigma and Lean.

2. UNDERSTANDING THE NEED FOR CHANGE (CHANGE OF THE STATUS QUO)

First step towards embracing Six sigma and Lean is to understand and accept the need for change. Despite its focus on quality, it is the fact that pharmaceutical industry has failed to keep up with other industries in terms of manufacturing efficiency and productivity, the main reason for this being high costs and burden involved in revalidating any process change, even

though changes were made in the spirit of improvement.

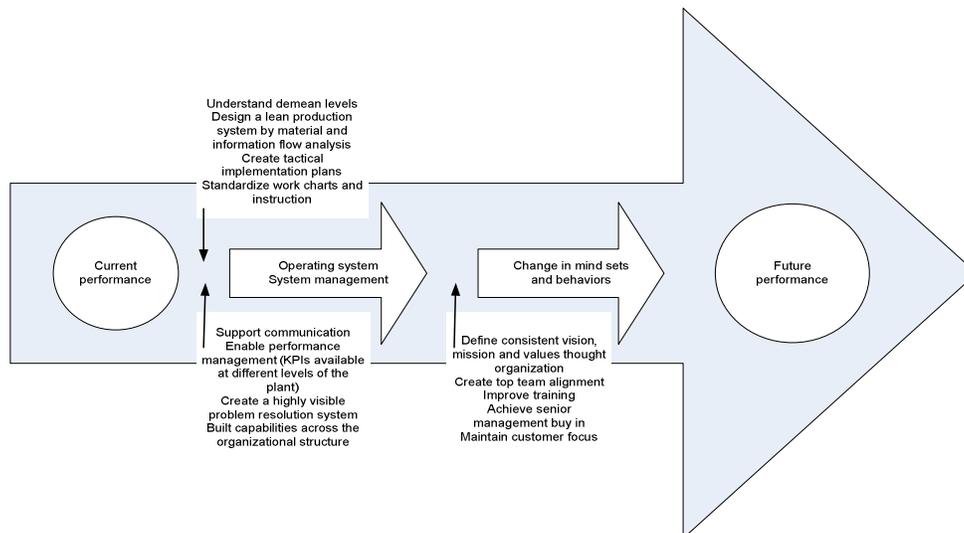
Pharmaceutical manufacturers reluctantly change processes which are confirmed and validated and accepted as complainant.

From the historical perspective, pharmaceutical manufacturers who had high profit margins had not enough economic stimulus to introduce changes. It is obvious that this situation has changed.

This already mentioned pharmaceutical industry's commitment on maintaining the status quo has produced inefficiency and increment in waste. It is estimated that the world wide potential cost savings from efficiency improvement in pharmaceutical industry could be as high as 90 billion dollars per year.

On the other hand it is a known fact that Research and Development are the major cost center in pharmaceutical companies, while manufacturing accounts for more than twice the expenses of R&D, representing around 36% of total costs.

The true costs of manufacturing become apparent when one considers the non value added activities and waste which represent 80% and 50% respectively. [4] Picture 1. show changes demanded for successful Lean transformation



Picture 1. Changes demanded for succesfull Lean transformation [4]

In the environment which does not accept changes consequences have impact on quality as well. Statistics show that the number of drug recalls has increased drastically on yearly basis, three quarters of which are attributed to manufacturing defects. The reject percentage in the pharmaceutical industry ranges from 5 percent to 10 percent (< 2 sigma), compared to 0.0001 (6 sigma) in the semiconductor industry. The reject percentage costs the pharmaceutical industry between 4.5 and 9 billion US\$ per year, which is quite a lot

compared to 90 billion spent on manufacturing.

Several important factors have led in recent years to substantial change in the approach and management of manufacturing operations in pharmaceutical industry. First, many manufacturers face the fact that they can not keep up with development pace and sustain competition from the part of generic drug manufacturers [4]. As such, they see a growing need to abandon the status quo and to focus on improving productivity, efficiency and quality.

At the same time U.S. FDA and other regulatory bodies have come to the conclusion that pharmaceutical industry has fallen behind other sectors in terms of efficiency and quality and based on that they have begun to endorse a “quality by design” model instead of current “quality by testing”. As part of this change FDA has launched its PAT (Process Analytical Technology) initiative, a risk based guidance model which is to direct pharmaceutical manufacturers toward consistent and predictable quality (higher sigmas). The PAT approach leads to rising of quality level through a deep understanding of variability of process parameters, which effect product quality from its very beginning.

In the past, pharmaceutical industry, for which the principles of Good Manufacturing Practice are mandatory, has slowly been embracing Lean manufacturing, in contrast to other sectors that adopted it relatively quickly and successfully. Therefore, in this article emphasis was put on the comparison of cGMP and Lean approach, identifying areas of overlap, as well as the challenges faced by pharmaceutical companies while turning to Lean manufacturing.

3. COMPARISON OF CGMP AND LEAN

GMP has evolved gradually, representing a complex system of rigorous rules and institutionalized tradition of drug manufacturing in order to ensure the safety, reliability and quality.

The current scientific risk-based framework and the process analytical technology (PAT) initiatives, developed by regulatory authorities to support innovation and efficiency in a cGMP environment, suggest a new way of thinking for the 21st century [5]. Since 2001, regulatory authority policies have promoted initiatives designed to increase the availability of new and affordable medicines. This new thinking should help the pharmaceutical industry move towards innovation in manufacturing and alleviate the fear of lean improvement. These fears will only be removed when manufacturers are confident that a successful lean implementation in a cGMP environment can have both regulatory approval and be technically dependable.

A comparison of cGMP with lean manufacturing (Table 2) might suggest that they belong to two conflicting families.

While cGMP focuses on manufacturing as a means to produce safe and effective products for the patient, lean focuses on manufacturing as a location for improvement and value creation from a customer's perspective. For example, the public's expectation for an aspirin tablet has changed very little in comparison with their expectation for a personal computer during the last thirty years. They still expect the tablet to be safe and effective, while they expect the computer to have improved and provide greater value in return for the price paid. In table 2. comparison of the most important attributes of Lean concept and principles of cGMP were shown.

Table 2. Comparison of the most important attributes of Lean concept and principles of cGMP in pharmaceutical production [5]

Area	LEAN	cGMP
Objectives	Reduce waste Create value	Ensure product effectiveness Prevent harm
Focus	Value stream	Product development, manufacturing and quality assurance
Approach to manufacturing	Quality balanced with productivity	Quality first
Improvement	Continuous and simultaneous	Regulated and prudent
Typical goals	Reduce cost Improve quality Reduce cycle time Reduce inventory Improve delivery	Follow validated process Prevent deviation
Typical tools	Value stream mapping Kaizen improvement Error proofing Moving to pull Simple flow Training Quality function deployment	Documentation Personal qualifications and training Cleanliness Validation and qualification Complaint review Audits

Lean's dual objectives, to reduce or eliminate waste and to create value, differ from cGMP's objective,

which is to ensure that all levels of control are in place to deliver a safe and effective medicinal product.

Perhaps where cGMP and lean do overlap is in a shared history in the control of the manufacturing environment.

To see the degree of overlap, a new perspective of lean, referred to as *lean pharma*, will be discussed [5].

Lean pharma

Lean pharma can best be viewed by looking across the lean landscape from a cGMP perspective. To do this, one has to define in simple terms what "lean" means [5].

Lean landscape

In 1999, Spear and Bowen identified four rules that describe the make-up of the lean manufacturing system [6].

- Standard work — all work must be specified as to content, sequence, timing and outcomes.
- Clear relationships and communications — every internal customer-supplier connection must be direct with unambiguous ways to send requests and receive responses.
- Simple flow — the pathway for every product and service must be simple, direct and followed.
- Scientific method — improvement should be made using scientific methodology, under the guidance of a teacher and at the lowest possible level in the organization.

They identified the lean manufacturing paradox; the existence of rigidly documented processes that operate in a flexible and adaptable environment.

It is the combination of being able to perform the simple things right, while also having the ability to change and adapt to customers' demands, which makes lean such a successful improvement methodology and business survival tool.

For the purpose of this article, it will be assumed that these four rules must be followed for a traditional manufacturing culture to reach the tipping point to transform into a lean manufacturing culture.

4. GMP PERSPECTIVE

One of the characteristics of a cGMP manufacturing environment is the abundance of documented processes such as standard operating procedures (SOPs), testing methods, environmental controls and training programmes.

This documentation can be divided into technical standards and operational procedures.

Technical standards, such as product specifications, validated settings and production conditions, can only change following a change control exercise. Operational procedures, such as the way people interact with equipment and the way that product flows, are based on custom and experience, and will change regularly in response to deviation or safety concerns. The essence of lean pharma is determining how current operational

procedures can be modified to support short-term improvement, while maintaining the technical standards — thus ensuring no risk to the product. An attempt is made to do this, from a cGMP perspective, for each of the four rules defined here [5].

Rule 1: Standard work

Standard work in lean manufacturing is an agreed set of work procedures that establish the best and most reliable methods and sequences for each process and employee. It is a detailed instruction on how a task can best be performed today, with the understanding that it can be improved tomorrow.

Standard work procedures are communicated simply and easily; more chart and display than paragraphs and pages. The employees who work with the process write the standard work procedures and their descriptions reflect what actually happens in the work place rather than what might happen. It is written after the manufacturing step has been optimized to ensure product quality is reproducible and product flow is continuous.

Standard work is desired because if you can standardize a process then you can control it; and if you control it, then you can improve it. This is the essence of this rule.

In lean manufacturing, every step in every operation is performed in a predictable manner. The time, sequence, outcomes and inventory levels for each step are specified. The work time to perform a task is independent of the operator, so if it changes (increases or decreases) a problem has occurred. This immediately alerts the team leader to a problem as it happens, thus ensuring real-time control.

Looking at the pharmaceutical industry, it may appear that standard work is already *in situ*, with SOPs, manufacturing instructions, testing methods and validation protocols. However, these documents are often written by team leaders or scientists following validation and are only updated in response to a deviation, safety or quality issue.

In the cGMP environment, critical specifications and technical standards are very well defined, deviations from which are obvious and thus action can be taken. Operational procedures, however, are often light on detail and as a result, variations in these may not be detected. For example, the way an operator sets up a workstation may vary with respect to time and outcomes.

A check sheet may ensure that critical steps have been completed, but the manner in which the end-result was achieved is not obvious. It is then possible for work variation to enter if people use slightly different methods to achieve the same result. Typical finished dose manufacturing working instructions may include "charge the blender...", "set up take-off plate".

In a lean pharma plant, SOPs and other manufacturing instructions would be viewed as a means to expose problems and encourage improvement.

Technical standards will be identified and fixed in line with regulatory requirements; all other operational procedures would be reviewed on a systematic basis and standardized with respect to time, sequence, content and outcome. For example, the batch manufacturing instruction could still contain the term "charge the blender", but the work standard for the blender would be written by the people who perform the action and would appear in a separate form, possibly as a chart or on-line display [5].

Key points:

1. cGMP and Lean overlap with a shared history in the control of the manufacturing environment
2. In a lean pharma manufacturing environment cGMP and Lean must be equal partners
3. FDA's PAT initiative is well aligned with Lean manufacturing

The challenge for the pharmaceutical industry in turning to lean is the design of new operational procedures that are consistent with all external regulatory requirements, but also support continuous improvement.

Rule 2: Clear relationships

In the lean manufacturing environment, every customer-supplier connection is direct with unambiguous ways to communicate. There is a clear and agreed way to send requests and receive responses. Product and information flows from one department to another and the barriers between departments are reduced. The overall goal is to keep product flowing. Consistent cycle time is an indicator of good internal supplier-customer relationships.

In the cGMP environment, product cycle time is quality driven; it may take longer to release a batch than it does to produce it. Different departments usually have clear individual responsibilities and objectives. Departments often have separate responsibilities and objectives, resulting in teams working in isolation or in conflict with one another. Individual departments are often unaware of the impact that their delays or problems have on overall product flow.

In the lean pharma environment, cycle time and quality would be of equal importance. This overlaps with FDA's PAT framework of reducing production cycle time. When a deviation in cycle occurs, it may indicate potential quality issues. For example, if it typically takes an operator 40 minutes to set up a tablet press but a batch takes longer, this indicates a problem with that batch. In lean pharma, a request for help would be made by the operator at 41 minutes, thus commencing an investigation.

The need to ask for help when product flow is interrupted may lead to the identification of quality issues that otherwise might have been hidden from view or only detected during final release. For example, when an operator in a traditional pharma plant is required to produce a tablet to a specified disintegration time, the

time it takes to set up the tablet press to produce tablets meeting the required technical standard is not controlled. In a lean pharma plant, the operator would have a work time standard. If it is not possible to produce the tablet to the required disintegration specification within this time, a call for help would be made. This may expose a problem in the upstream process, in this case granulation, which would otherwise be masked.

The challenge for pharma in moving towards lean is to reduce the grey zones of responsibility, slow response and late calls for help when problems occur, and move towards an environment where problems are immediately identified, shared and resolved across the plant.

Rule 3: Simple flow

In lean manufacturing, the pathway for every product and service must be simple and direct. Simple in that there is only one way to move forward and direct in that there are no loops, forks or fast paths.

In the cGMP environment, the product path tends to be direct but far from simple because of batch manufacturing. This batch production method is inherent in cGMP to prevent cross-contamination. Each process step usually has a holding time for work in process, thus encouraging intermittent flow. Typically, a pharmaceutical facility operates with surplus capacity to keep the product moving, rather than flowing; however, this operational mode obstructs simple flow. For example, when a batch of tablets is scheduled to run on a blister pack line and three lines are available, surplus capacity at packaging exists. This will hide the reasons for any excessive downtime and slow changeover on the lines.

Having available surplus capacity does not encourage continuous improvement or problem identification. From the customer's perspective, the fact that a pharmaceutical plant is running with surplus capacity should have little consequences in the short-term. The product will still be delivered on time, at the right quality and in accordance with cGMP, but the plant with surplus capacity available has higher operating costs.

In the lean pharma plant, product or services would not flow to the next available person or tool, but to a specified person or item of equipment. This rule enforces the economies of repetition — the more times you take a certain path the more familiar you are with that path. Each time the product takes the same path, an experiment will occur to uncover variation and expose problems. This encourages continuous learning over the life cycle of a product.

A batch moving from manufacturing to finished goods would only slow down for a value adding step. There would be a continuous programme to reduce batch queues and a move towards small-scale equipment to improve efficiency and manage variability. In lean pharma, the focus would be to reduce

your batch size, move towards single unit flow, and thus improve responsiveness to changes in customers demand.

The challenge for pharma in moving towards lean is to introduce simple flow for products and services and expose areas where improvement in flow will reduce cycle time and cost. To move forward from batch manufacturing towards single unit flow.

Rule 4: Scientific improvement

The first three rules are project rules, which show how to set up operations as experiments, with an expectation to control the process and to ensure it is reproducible. The fourth is the rule on improvement. Once you can do the job consistently every time, then you can improve. Attempting to improve a process that has too much variation often makes the process slower or reduce the effect of any improvements.

In lean manufacturing, the scientific methodology is the driving force to total quality. Without this, the manufacturing process is too variable and unstable to enable the introduction of a lean manufacturing philosophy [7].

The cGMP environment is already rich in science. Science is used to develop the batch manufacturing process, support laboratory testing and evaluate product release to market. The employees who "handle" the product have a defined role, which is to produce product in a controlled and consistent manner.

Traditional improvements in the cGMP

environment come out of reaction to deviation rather than from the need for variation reduction. The fear of change and the current systems to control it, together make continuous improvement very difficult. However, some pharmaceutical plants already operate with well-controlled and optimum processes. For these plants the move towards lean should not be such a challenge.

The challenge for the pharmaceutical industry in moving towards lean is to implement FDA's risk-based approach, which is firmly based on science and engineering principles.[8]

5. CONCLUSION

In a lean pharma manufacturing environment, cGMP and lean must be equal partners. The cGMP standards together with lean principles must be embedded into the culture of an organization and the business strategy must reflect this. This challenge is less problematic because of recent changes in regulatory thinking. The principles of FDA's PAT initiative appear to be extremely well aligned with lean manufacturing thinking, suggesting a positive outlook for lean pharma, which has successfully been implemented in companies such as Astra Zeneca, Johnson & Johnson, Pfizer and others.

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