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REVIEW

Change Control System in the Pharmaceutical Industry in the Lean Thinking Concept

FERNANDES F*, PANDE S**, MURTY P N***

* M. Pharm, (PhD) Pharmacy, Behrampur University, **Senior Vice President, Corporate Quality Assurance, Glenmark Pharmaceutical Limited, Mumbai, ***Principal and Professor of Pharmacy, Royal College of Pharmacy and Health Sciences, Behrampur, (India).
Corresponding Author:
Francis Fernandes
E-mail: fransha.ape@gmail.com

Change control is one of the critical elements in a pharmaceutical or biotech company's quality management system. Inadequate change control procedures end up creating a huge risk of non-compliance. The change initiatives are aimed at improving quality, increasing yield, reducing costs, cutting waste, streamlining processes etc. It would be very difficult to carefully manage and expedite change control in a large company or a fast growing organization without a six sigma or Lean thinking concept.

The challenge that Quality Assurance Managers are facing today, is on how to keep pace with rapidly changing regulatory needs, and at the same time, to increase output with limited resources. Pharmaceutical Quality systems can earn more profit from learning to think in terms of Lean, a philosophy that aims to eliminate waste. Based on a customer-focused view, six steps can provide a strong foundation for any organization that wants to incorporate Lean into its operating philosophy. These steps in Lean thinking can be best evaluated at the producer end by Authenticating and reviewing each step, one at a time.

1. Value
2. Value Stream
3. Flow
4. Pull
5. Perfection
6. Replication

Lean thinking can best start by giving due consideration to value, which ultimately is the customer's requirement. The value of any product (goods or services) is defined by customer needs and not by any non-value-added activity at the supplier's or producer's end. That is, the customer is prepared to pay for the operations by producers or their suppliers that transforms the product in a way that is meaningful to the customer. Customers do not want to pay for "waste at the producer's end".

1. Value (Specifying)

Value is determined by the customers who want to buy the right product with the right quality at the affordable price. That is, the product must be "right" every time – from design to manufacture and from delivery to error-free operation. Lean works on making their processes right by eliminating waste – something no customer wants to pay for.

In Case of Pharmaceutical Products, value defined by the FDA (customer) for drugs is contained in five types of documents utilized by the FDA to ensure that the manufacturer's products are safe, effective and have the identity and strength to meet the quality and purity characteristics as intended: FD and C, 21 CFR and Federal Register, CPGMs, other manuals, and Human Drug cGMP Notes issued by the FDA. While generally linking the term "value" with the Change control

management system in Pharma, in accordance with the FDA documents referenced above and industry standards, the following components are to be reviewed for the value for the customer, as it relates to any specific change.

The Change control system evaluates and approves proposed Minor, Major, and Critical 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). It also approves the implementation of new equipment and systems, as well as evaluates, approves, and determines the quality release requirements for repairs to facilities, equipment, and systems that could impact product quality.

2. Value Stream Mapping (Identifying)

Once the value is specified by the customers, the next Lean step is to identify the right process – a process that only adds value to the product: in other words, a waste-free process. The value stream for a product has three categories of activities:

a. Process steps that definitely create value: In any manufacturing process, the steps that actually transform the fit, form or function of the raw material, and bring it a step closer to the finished product.

b. Process steps that create Sub value but are necessary due to the current state of the system: In any manufacturing process, activities like inspection, holding and transportation steps.

c. Process steps that create no value and can be eliminated: Any activity that does not fall into the above two categories.

While the parts of a process that create no value should be eliminated, any action or activity that is recognized as non-value-added, but is currently necessary, should be targeted for improvement. At this point, a detailed process flow diagram should be generated for each product or product category. To ascertain as to which steps in the process are unnecessary or can be improved for better productivity, an intense questioning and re-examining method (Japanese term is *kaikeku*) should be applied to every aspect of the unit process under consideration.

This change control component consists of a value stream and sub-value streams as appropriate for minor, major and Critical changes. There are value streams for repairs, changes or modifications and new introductions of manufacturing equipment, control systems, critical systems, support systems, facilities in the 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 the change control
- Present the proposed change to the Change Control Board (management representatives of regulatory affairs, change control, engineering, environmental health and safety, Head of manufacturing, validations, quality auditing, laboratories, technical

support, quality operations, and the Head 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 the acceptance of the proposed change and target the 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 the computer system or PLC if required, for equipment operation
- Generate stability data, probably with accelerated aging stability test results as applicable, for release of the product produced with the new process
- Generate all required new documentation (procedures and forms for operation of the equipment and training documentation, cross-reference of the new process validation in the 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, customers and other facility notifications, stability requirements, material qualifications, new drawings and updates and include in change package .
- Generate a 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-implementation approval effectiveness
- Close and file the change request package.

3. Flow

This Lean step focuses on rapid product flow (RPF). The specific process waste is identified at each stage of the process flow and is eliminated. The team involved in Lean will physically walk the process and write down the distance that the product travels during its process flow. The non-value-added distances are eliminated by

physical layout change, which involves both human and machine. Factory floors are laid out in cells rather than in functional groupings, which reduces the distance that the parts travel in the process flow.

It is at this point that the Lean enterprise implements 5S, a tool which is developed for reducing the slack hidden in the manufacturing processes. 5S is the basis for Lean manufacturing and the foundation for a disciplined approach to the clean workplace. The five steps of 5S are (in Japanese and English):

1. *Seiri/Sort:* Meaning sorting or segregating through the contents of the workplace and removing all unnecessary items.
2. *Seiton*/Straighten: Meaning putting or arranging the necessary items in their place and providing easy access by clear identification.
3. *Seiso*/Shine: Meaning cleaning everything, keeping it clean and using cleaning to inspect the workplace and equipment for defects.
4. *Seiketsu*/Standardize: Meaning creating visual controls and guidelines for keeping the workplace organized, orderly and clean: in other words, maintaining the *seiso*, or shine.
5. *Shitsuke*/Sustain: Meaning instituting training and discipline to ensure that everyone follows the 5S standards.

Flow from change control 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 delay in any or all of the required activities of the sub-value stream. These delays result in the slow implementation of changes or improvements, increased costs, and increases in the potential compliance and business risks.

4. Pull

The benefits of Lean Steps 1, 2 and 3 allow a company to produce more than before and in a way that value is added at every step in the production process. The fourth Lean step can be directed towards either removing excess capacity (inventory) or increasing the rate of pull.
Lean, which identifies the seven wastes, are defects, over-production, transportations, waiting/holding, inventory, motion and processing (or the acronym, DOTWIMP). This lists the inventory as a source of waste. Hence, producing anything that is not sold immediately and is waiting at any point of time for delivery is waste. A pull system, which on the production side is making a product at the same rate at which it is being sold, is a waste-eliminating step. On the supply side, a pull system is flowing resources into a production process by replacing only what has been consumed.

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 the new equipment and processes that interact with the existing systems and processes are difficult to isolate. There is a potential negative impact to the existing systems and processes, potential that the new equipment and process will be used inadvertently prior to authorization, and potential of the 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.

5. Perfection

This Lean step emphasizes that continuous improvement has to be a part of the organization and is always possible. This is the desired state of any change in any environment. The organization should always try to achieve what is the perfect system for that kind of operation and should aim at continuously improving the present system. The word for this in Japanese is '*kaizen'*.

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.

6. Replicate

This Lean step is a confirmation of the system implemented and the improvements achieved that determines that these same systems, procedures, tools and techniques can be deployed anywhere in the operation or in any business process. The key benefit of this step is that any time spent in analysis is reduced.

Now is the time to ask these questions:

- How will the team ensure that the business learns from its experience?
- Can this process improvement be replicated in other parts of the business?
- Is the control set true enough for a similar type of operation?

Hence, finally it can be concluded that each of the processes involved in the quality systems of Pharmaceutical, Biotec or CRO companies has some element of waste. Utilising Lean philosophy, the "wastes" in the complete cycle of the Change control system can be identified and eliminated or improved upon in order to have a better Quality system and overall efficiency with a net result of increased compliance. However, any waste elimination or process improvement proposal should not impact the basic principles of the product's identity, safety, efficacy, purity or FDA requirements.

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