

*Chapter 6*

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**Operational  
Excellence**

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## Objectives

This chapter provides an introduction to the role that Operational Excellence (OPEX or OE) plays in the continuous improvement of biomanufacturing operations. The chapter is not intended to serve as a comprehensive guide to every quality improvement, but rather as an overview of tools and techniques which illustrate many of the basic principles of Statistical Process Control (SPC). SPC is a methodology that uses statistical tools and analysis to monitor variations in a process in order to manage and control it.

After completing this chapter the student will be able to:

- describe a process
- identify potential sources of waste in a process
- define when a process is “in control” versus “out of control”
- explain the simple tools used in Lean and Six Sigma improvement methodology
- list the steps in a Six Sigma process improvement
- select and apply general Lean Six Sigma tools to simulated problems
- recognize deployment challenges to OEX strategies

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## Terms

**5S (Sort, Straighten, Shine, Standardize, and Sustain):** a workplace discipline used to ensure reliable work practices and a clean working environment; used in the West but originally from Japan. The term 5S is derived from the original Japanese usage of S-prefix words: Seiri, Seition, Seiso, Seiketsu, and Shitsuke.

**Andon:** a visual management tool and component of the lean philosophy; these are lights placed on or adjacent to machines or production lines to indicate operation status.

**Correlation:** a statistical relation between two or more variables such that systematic changes in the value of one variable are accompanied by systematic changes in the other.

**$C_{pk}$  (Process Capability Index – Does not assume process is centered between specification limits):** a calculated value used to compare process variation to a specification; this can also be used to compare processes.

**DMAIC (Define, Measure, Analyze, Improve, and Control):** a method which can be considered as a continuous improvement process in its own right; based upon statistical analysis, it aims for systematic elimination of all non quality sources.

**DOWNTIME:** a term to remember the different sources of waste to be eliminated through lean manufacturing practices. The acronym derives from Defects, Overproduction, Waiting, Non-Utilized talent, Transportation, Inventory, Motion, and Extra processing – each of which represents a source of waste in a process.

**F-Test:** a statistical test to determine if the variances of two populations are different.

**Failure Modes and Effects Analysis:** a systematic approach to risk identification and analysis wherein possible modes of a process or equipment failure are identified and their consequences, should they occur, are analyzed. Ultimately, this helps to prioritize remediation efforts.

**Fishbone Diagram:** a problem-analysis tool that derives its name from its shape, which resembles the skeleton of a fish; also known as a Cause-and-Effect diagram or Ishikawa diagram, named for its inventor, Kaoru Ishikawa.

**Flow Chart:** a pictorial summary that illustrates with symbols and words the steps, sequence, and relationship of the various operations involved in the performance of a function or a process, usually temporally.

**Gemba:** a Japanese word meaning “the place where it happens” or the place where real action occurs—where products or services are performed. In a manufacturing environment the gemba often refers to the shop floor, since it is there that products are transformed into customer value.

**Heijunka:** a Japanese term meaning “leveling”; Leveling the type and quantity of production over a fixed period of time. This enables production to efficiently meet customer demands while avoiding batching, which results in minimum inventories, capital costs, manpower, and production lead time through the entire value stream.

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**Kaizen Event:** The term “kaizen” itself is Japanese for “good change”. Thus a kaizen event is the application of kaizen techniques in an accelerated manner that focuses on a specific improvement area.

**Kanban:** A Japanese term meaning simply “signboard”; a communications tool in the “just-in-time” production and control system; A kanban is attached to specific parts in a production line and signifies the delivery of a given quantity, or can be used at inventory storage sites to identify how many of each part should be on-hand.

**Lean Manufacturing:** the term ‘lean’ was coined by John Krafcik in a 1988 article in the *Sloan Management Review* and referred to Toyota’s production system. Lean is a business philosophy and/or strategy that focuses on eliminating waste—all steps or processes that do not add value to the final product or service.

**Pareto Chart:** named for Italian economist Vilfredo Pareto, it is a special type of bar chart, where frequency values are arranged in descending order, and a superposed line plot tallies the cumulative total of the bars’ values. The Pareto chart is one of the 7 basic tools of quality.

**Poka Yoke:** a Japanese term which translates roughly to “mistake proofing” it is a technique of preventing errors from occurring by designing the manufacturing process, equipment, and tools in such a way that it becomes difficult to perform activities incorrectly.

**Product Lifecycle:** the complete life of a product, from early planning through sales build-up, maximum sales, declining sales, and withdrawal of the product; product life cycle lengths and types can vary depending on the type of product, the frequency of replacement, and other factors.

**Six Sigma:** a systematic method for improving the operational performance of an organization by eliminating variability and waste (sigma stands for standard deviation from the mean in a normal distribution).

**Spaghetti Diagram:** a map depicting the movement of people, product, or materials and total distance traveled; able to depict multiple people.

**Standard Deviation:** measure of how widely values are dispersed from the average value (mean).

**Statistical Process Control (SPC):** the application of statistical methods to the monitoring and control of a process to ensure that it operates at its full potential to produce conforming product.

**TRIZ:** a Russian acronym for Teoriya Resheniya Izobretatelskikh Zadatch (translates to “Theory of Inventive Problem Solving”; a technique that attempts to define a specific problem as a system and identify elements in the system that need correction to reach the desired solution. TRIZ at its most basic level strives to not create new solutions based on improvements on existing solutions, but to look at problems in new ways.

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**T-test:** a statistical test used to determine if the means of two groups differ; for instance, a t-test could be used to determine whether writing ability differs among students in two classrooms.

**Value Stream:** the chain of activities which transform process inputs into customer value (a finished product or service). To be value-added in this context, an activity must: 1) Not require re-work (i.e., be executed 'right first-time'), and 2) Transform the product or service in a way the customer is willing to pay for.

**Value Stream Map:** Value Stream Mapping is a lean manufacturing technique used to analyze the flow of materials and information currently required to bring a product or service to a consumer; at Toyota, where the technique originated, it is known as "material and information flow mapping," because it contains not just a depiction of processing steps, but also the information flows required to execute each step.

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# Introduction to Operational Excellence

## Overview

The biomanufacturing industry is a very complex industry. Bringing a biopharmaceutical product to market can take many years of development to determine the viability of a safe and effective product. Many factors impact a biomanufacturing organization's success from development to licensing to commercial production. These factors include:

- research and development
- administrative and financial support
- quality efforts
- safety, health, and environmental programs
- facilities construction
- equipment
- infrastructure (computer networks, etc.)
- personnel salaries
- raw materials
- utilities
- maintenance
- transportation and distribution
- sales and marketing

It is a challenge for an organization to develop a safe, effective, pure, and high quality product while still trying to ensure the lowest cost to the consumer as possible.

One way to contain costs while maximizing product quality is through a business approach called Operational Excellence (also referred to as OPEX or OE—OE will be used in this textbook). Operational Excellence is a guiding business philosophy which requires an organization to continuously strive to achieve excellence in all aspects of its operations, adding value to its business. Manufacturing industries, including biomanufacturing, use OE's efficiency methods and data-driven decision making process as part of their daily operations.

## Background on quality efforts and their influence on Operational Excellence

### Modern era

Modern iterations of quality systems are numerous, as quality management systems have evolved into a defined scientific discipline. Constant changes in business, industry, and social cultures have aided the development of quality practices. These practices are continuously evolving to keep pace with the present state of both business and life.

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Conceptually, many of lean manufacturing's principles can be traced back to Benjamin Franklin, who wrote "a penny saved is two pence clear. A pin a-day is a groat [coin]-a year. Save and have." One of the recognized leaders of quality innovation and just-in-time manufacturing, Henry Ford, cited Benjamin Franklin as a major influence in his thinking about efficient production.

In 1910, Fredrick Taylor was responsible for initiating the shift from the physical inspection of produced goods to the use of data to accomplish the same when he published the book *The Principles of Scientific Management*. Taylor was responsible for expanding the current inspections to encompass product specifications, standards, procedures, detection, tests, and other activities that comprise the fundamentals of today's quality systems.

Taylor's work was followed by the work of Bell Labs. In the 1920s, the organization began utilizing statistical methods such as Walter Shewhart's Statistical Process Control charts and Dodge-Romig acceptance sampling charts. Shewhart's work showed that reducing variation in a manufacturing process was vital, and he introduced a tool called a control chart as a tool to help reduce such variations. Harold Dodge and Harry Romig's acceptance sampling involves selecting a sample of a product at random from a batch or lot and testing it; based upon the information from the sample, the quality of the batch/lot as a whole could be inferred and a decision could be made as to whether it should be accepted or rejected.

In the 1940s, quality gurus Joseph Juran, Edward Deming, and Mitchell Feigenbaum were invited to Japan to help improve the country's poor product reputation. In the 1950s-70s, the Japanese embraced the teachings of these gurus to rebuild their economy after World War II. By the 1980s, Kaoru Ishikawa's cause and effect diagrams and Genichi Taguchi's experimental design methods became major tools in the quality system tool box and are still in use today. Later sections in this chapter address the influence the Japanese have had on quality and consequently OE.

The name of the quality system movement has changed over the decades. For example, in the early 1960s the term *Quality Circles* was used. This approach valued workers, who were given a voice to address quality issues. In the 1970s the name changed to *Total Quality*, a program in which company-wide quality control involved all workers from top management to the production line.

In the 1980s and '90s the initiative was referred to as *Total Quality Management (TQM)*. TQM is a management philosophy and operating approach that aims to consistently exceed the current and future expectations of all stakeholders of a process.

From the late 1980s to the present, new vocabulary emerged to describe the changing quality movement as it developed. Terms such as *Reengineering*, *Six Sigma*, *Toyota Production Systems*, and *Lean* are included in the quality movement lexicon. Professional and organizational certifications have been established to recognize and promote excellence in quality. Organizational certifications, such as ISO 9001 and the Malcolm Baldrige award, are pursued by businesses and industries. An organization's staff members can seek individual certifications such as Lean Master, White, Yellow, Green, Black, and Master Black Belts. The belting practice was developed by Motorola in the 1980s as a way to symbolize level of

understanding of quality improvement principles, and was designed to mirror the different belt colors used in the martial arts (where white belt typically signifies beginner rank, and black belt symbolizes expert rank).

While the names of the quality movement have changed over the past 100 years, the goal is the same: to provide a quality product that meets and/or exceeds customers' expectations and needs. If history is any indication of the future, the names of the quality movement – and the supporting tools – will continue to progress and change. The principles and spirit of the quality movement, however, will remain.

## Business of Biomanufacturing

OE efforts have a place within all levels of a biomanufacturing organization. When the organization announces its strategic evaluations of its overall performance metrics, it can use an OE tool referred to as a balanced scorecard. This tool captures and easily displays multiple dimensions within an organization's performance. Balanced scorecards can help stockholders, employees, and even regulatory agencies view a "snapshot" of an organization. Figure 6-1 depicts a sample balanced scorecard for the Corporation Metrics for "ABC Biomanufacturing, Inc." Color-coded cells on the chart indicate Exceed Target (green), At-Target (yellow), and Missed Target (Red).

CORPORATION METRICS: ABC Biomanufacturing, Inc.					
Metric	1Q	2Q	3Q	4Q	YTD
Revenue	+	+	+	0	+
Net Income	0	+	+	+	+
Warning Letters	+	+	+	+	+
Back Orders	0	+	+	+	+
New Products	-	-	0	0	0

Figure 6-1. Balanced scorecard for "ABC Biomanufacturing, Inc."

Operating units and departments within the organization can also create their own balanced scorecards using their own metrics. In Figure 6-2, employees in the Fermentation Unit cannot control the organization's net income, but it can control "scrap," which affects the Unit Manufacturing Cost (UMC); this in turn impacts the organization's net income.

Fermentation Dept. ABC Biomanufacturing, Inc.					
Metric	1Q	2Q	3Q	4Q	YTD
# Batches	+	+	+	+	+
Scrap	+	+	+	+	+
Right First Time	+	+	+	+	+
On-time Mfg.	0	+	+	+	+
New Products	0	0	0	0	0

Figure 6-2. Balanced scorecard for "Fermentation Dept. ABC Biomanufacturing, Inc."

A balanced scorecard is just one type of OE tool. These tools can help reduce waste, increase efficiency, and reduce process output variation and maintain control. Before expanding upon OE and its various types of tools, an understanding is required of a fundamental aspect of biomanufacturing: the process.

### What is a Process?

Almost every aspect of one's daily life can be defined as a process, even though they actually occur as a continuum; from getting up in the morning and driving to work, to returning home and making dinner. These activities are performed in a particular order that leads to a desired outcome. In the case of driving to work, activities (steps) of the process can include opening the door, adjusting the seat or mirror, starting the engine, checking the rear view mirror, backing out of the driveway, etc. The desired outcome is that the driver arrives safely and on-time. In preparing a meal, the activities can include selecting a recipe, gathering the ingredients and cookware, preparing the ingredients, etc. The desired outcome is that all the food is on the table and ready to eat at the appropriate time.

The same holds true for processes in biomanufacturing. Raw materials are purchased from vendors. Preparations are made to produce the biological products. Solutions are made and

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organisms are used to produce beneficial molecules, which are then refined and packaged for commercial use.

Any process can run either efficiently or inefficiently, relatively speaking. During the drive to work, vehicle trouble could cause a delay. At mealtime, one of the side dishes may not be ready at the same time as the main course. What has gone wrong with these processes to affect the desired outcome? These processes should work correctly, but something has interfered with the intended result. There was inefficiency in the process. Did the driver not change the oil as recommended? Did the cook not realize the side dish took fifteen minutes to prepare instead of five? The next section of this chapter explores process efficiency through the focus of Lean Manufacturing.

## **Lean manufacturing**

The term “lean” was coined by John Krafcik in a 1988 article in the MIT *Sloan Management Review* entitled “Triumph of the Lean Production System.” Lean defines itself in the context of efficiency and effectiveness. For these purposes, *efficiency* is defined as ‘doing things right’ and *effectiveness* is defined as ‘doing the right things’. Note the subtle difference here – it is possible to perform activities correctly (efficiency), but they may not be the activities that a customer is willing to pay for! Alternatively, one could perform the proper activities (effectiveness) from a paying customer’s perspective, but not execute these activities well. Lean concerns itself with the balance of the right activities (effectiveness) done properly (efficiency). The most important concept in lean manufacturing is the understanding of delivering value to the customer and the elimination of waste in any form.

### **What is waste?**

Waste is any activity that does not add value to the customer. In the example of cooking a meal, waste includes preparing too much food, burning the food, using too much seasoning, etc. Because of these activities the food is wasted.

In biomanufacturing, the acronym DOWNTIME, a helpful mnemonic, spells out some examples of waste:

- **D**efects, or rework due to errors or non-conforming material
- **O**verproduction, or producing more than what is needed
- **W**aiting, or waiting on documents, signatures, deliveries, etc.
- **N**on-utilized talent, or under utilizing the ideas, skills, and talents of the workforce
- **T**ransportation, or any non-essential transport
- **I**nventory or material/product waiting to be processed but sitting in storage
- **M**otion, or any motion that does not add value
- **E**xtra processing, or the use of resources that are not required

Waste can be found almost everywhere if one looks hard enough.

### **What is value?**

Some process activities common to biomanufacturing are controlled by legislation or regulatory bodies, such as the FDA, EPA, and the Department of Agriculture. These agencies can require

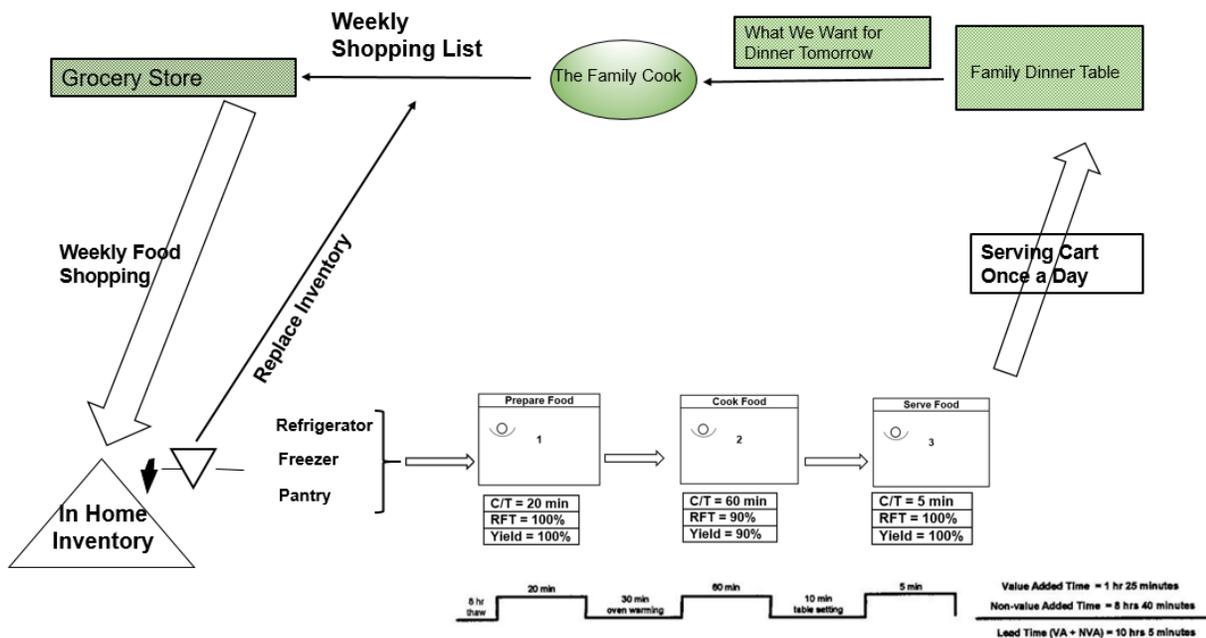
inspections, testing, sampling, and reports, which are examples of what is termed Necessary Non-Value Added (NNVA) activities. However, these are required processes and must be performed in order for the products to be approved for distribution.

Thus if reporting and inspecting are examples of NNVA activities, what is considered value-added work in biomanufacturing? Value-added is defined as either activities for which customers are willing to pay or activities that increase the form or function of the product or service.

Examples of value-added activities include items such as feeding the cells, purifying the effective molecules, packaging, and shipping the final product. Non-value added examples are activities that are wasteful, such as waiting for raw materials to arrive from the vendor, repairing defective equipment, correcting paperwork mistakes, etc.

A useful tool to differentiate value-added from non-value added work is called a Value Stream Map (VSM). The VSM is a tool that assists in understanding the flow of material and information as products make their way through the manufacturing process.

Figure 6-3 depicts a Value Stream Map for preparing a meal. Raw materials come in from the grocery store, which should be the right ingredients in the proper amounts. The major processing steps are Preparing, Cooking, and Serving.



**Figure 6-3. Value Stream Map for preparing a meal**

In the meal example, the family expresses the desire for a particular menu to the family cook. The cook, in turn, prepares a weekly shopping list and purchases items at the grocery store. Grocery inventories are stored at home in the freezer, refrigerator, and pantry. To prepare the

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meal, the cook checks the recipe and pulls the appropriate ingredients from the storage location. The meat for the main dish will need to thaw for 8 hours before being prepared.

It takes approximately 20 minutes to prepare the ingredients before they are cooked (Prepare Food step). Actual cook time in an oven for the main dish is 60 minutes (Cook Food step), but the oven needs to preheat for 30 minutes. Thus the actual cooking time is 90 minutes. It takes ten minutes to set the table for the meal. Finally, the prepared food is placed on serving trays and brought to the table, which takes five minutes.

The lead time (total duration time of the process) is 10 hours and 5 minutes, of which 1 hour and 25 minutes adds value to the meal (the total from the troughs on the time chart). Eight hours and 40 minutes is non-value added time (from the baseline of the time chart).

To make this process lean, one would look for ways to reduce the thaw time, the oven warming time, and the table preparation time. This would decrease the lead time (total duration) of the process. To this point, our efforts are concentrated on activities that add to the meal. The lean analysis involves what is happening to the food, not what is happening to the people eating the food.

### **What is an efficient workplace?**

Running an efficient kitchen, like running an efficient biomanufacturing facility, requires a balanced flow of materials and information. Flow involves having the right items available at the right time so that work can be done properly the first time.

#### **Visual workplace**

Referring to the meal example, it is important to know what food is in the house before the cook prepares the weekly shopping list. Purchasing items already on hand would be wasteful; not purchasing something required would be a problem. In a lean environment, a practice used to manage flow smoothly and quickly is called a Kanban system.

**Kanban** is a Japanese word that means “signboard.” A Kanban is a signaling system to trigger actions, like reordering supplies. Another visual cue device is an **Andon**, or “lantern” in Japanese. This is a warning light that can indicate an abnormality, quality problems, or material shortage. An everyday example of an Andon is the oil light in an automobile. In today’s workplace, visual communication tools can be computer screens that display process conditions or printed charts/data (Figure 6-4).

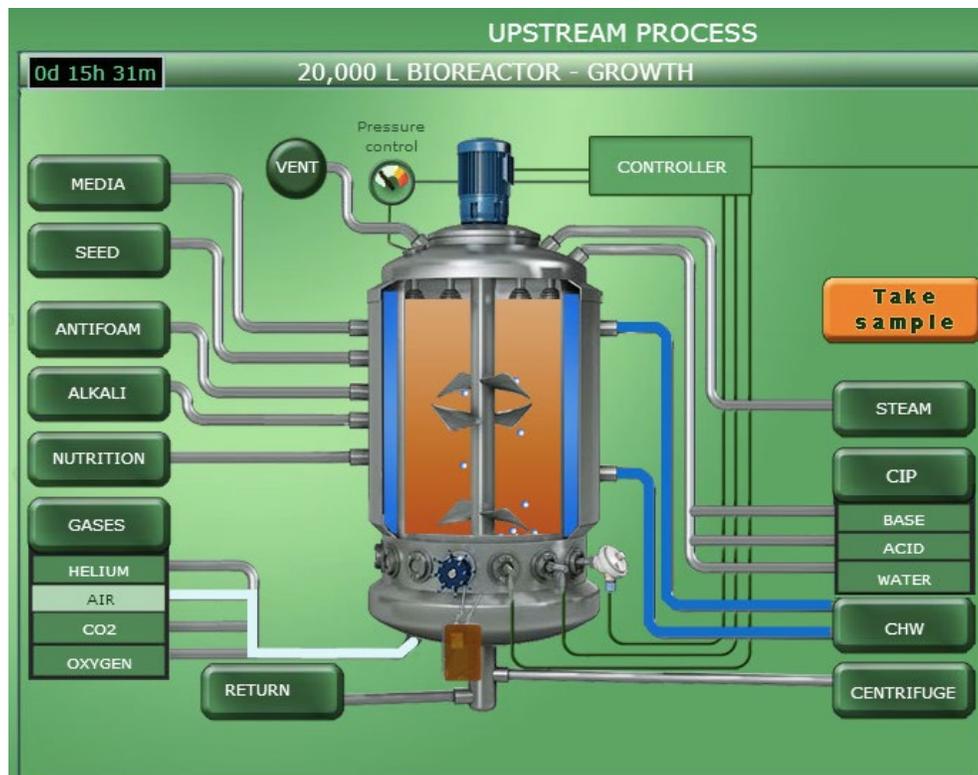


Figure 6-4. A Schematic Representation of a Computer screen depicting process conditions

### Balanced flow

In a lean workplace, great care is given to the balance of work at each step in the process. If some steps in the process take a short period of time to perform and others much longer, “bottlenecks” can develop. Bottlenecks are points in the process where inventory “backs up” and employees who have completed their assignment become idle. The Japanese word for “leveling” the workload is **Heijunka** and is a key feature of a lean manufacturing environment.

To balance a workflow and prevent bottlenecks, most lean manufacturing organizations institute a “pull system” for materials. A pull system is a flexible and simple method of controlling and balancing resources. The result of a pull system is the reduction of waste. Elements of the pull system include:

- production balanced with actual consumption
- bottlenecks eliminated at workstations or units
- small lots/reduced batching
- management by sight (visual workplace)
- enhanced communication between all levels of employees

### Clean, orderly, and operationally-ready

A lean workplace is an organized environment. In lean terms, the **5S** principle is a discipline designed to reduce waste and optimize productivity. A well-executed 5S program can provide

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upwards of 20% productivity improvement in an area – this is equivalent to a team of 5 being as productive as if having an additional member! 5S maintains an organized and standardized workplace by instituting the following:

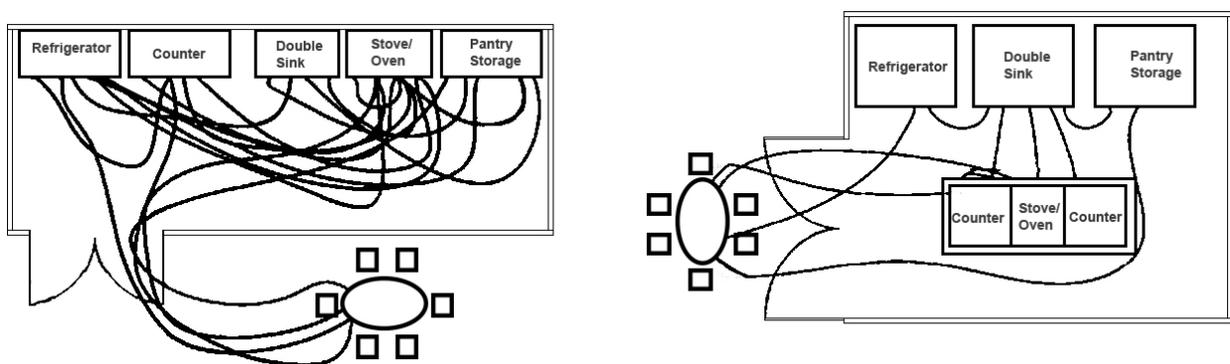
- **Sort:** keep only what is needed in the work area
- **Set in Order:** a place for everything and everything in its place
- **Shine:** inspect and clean the work space
- **Standardize:** develop rules to maintain order
- **Sustain:** follow the rules to hold the gains

Recently “Safety” was added as a sixth "S," however the principle is still widely recognized by its original name, 5S, though this is changing.

Principally, the role of 5S is to allow an area to be operationally ready and to identify and reduce wastes. The more organized and operationally ready a workspace is, the easier it is to identify outside-of-normal conditions. 5S is an important concept for employees to work efficiently and effectively. Organizing the work place is not only useful in manufacturing but can also be applied to laboratory and office environments.

### Smart design

Another principle of a lean work environment is where movement (the 7<sup>th</sup> waste in the DOWNTIME acronym) is kept to a minimum. In a well-designed kitchen, the cook is able to reach all the items and equipment needed to prepare the meal in a few steps. Items used most frequently are kept within arm’s reach and at the proper height to prevent wasted motion and possible injury to the cook (such as overreaching and straining a muscle). The same design principles are used in a lean workstation environment. Studies are often conducted to determine traffic patterns within a work space so as to arrange items to prevent unnecessary movement. A spaghetti diagram (Figure 6-5) illustrates how a poorly designed workstation causes unnecessary movement. The diagram also illustrates how to modify a workstation to increase productivity, improve safety, and reduce waste.



**Figure 6-5. Spaghetti diagram of a galley-style kitchen with an inefficient flow and a U-shaped kitchen with a more efficient flow**

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## How to deploy lean improvements

**Kaizen** is a Japanese word that means “good change.” Organizations apply this principle by conducting a Kaizen event, which is a structured project aimed at identifying defects and systematically removing waste and non-value added activities; the event is completed in a relatively short amount of time. Kaizen events typically include the following activities in the order in which they are listed:

- **gemba**—management visits the actual workspace and observes employee activity
- planning and preparations are made for the commencement of the Kaizen event
- a cross-functional team is formed to participate in a kaizen event to solve the problem; the event can last from three to five days
- after the implementation of improvements (the duration of which ranges from several days to several months), the work is standardized to hold the gains made

## Six Sigma Process Improvements

Processes that have been made as lean and efficient as possible may still fail to achieve the desired results. One popular methodology used to increase quality in such a situation is a Six Sigma process improvement. This approach focuses on reducing process variation and striving for what is called a ‘Six Sigma’ level of control. (sigma refers for standard deviation from the mean in a normal distribution).

### What is process control?

To understand Six Sigma, it is necessary to discuss process control as it relates to quality efforts.

Through lean manufacturing practices, businesses can run efficient production systems and make rapid improvements during kaizen events. However, an efficient system that produces inferior products is destined to failure. A biomanufacturing operation must produce products that meet quality specifications over time. Any manufacturing process not capable of producing a consistent product is considered to be “out of control.”

Process control partly involves a series of improvements designed to reduce variation and ensure the quality and consistency of biopharmaceutical products. Tools and techniques used to reduce variation are generally considered to fall under the heading of Six Sigma process improvements.

### What is Six Sigma?

Six Sigma is a quality management program that uses statistical methods to reduce variation and eliminate defects in business or manufacturing processes. The term *Six Sigma* was coined by engineers at Motorola in the 1980s to describe a level of process quality that produces no more than 3.4 defects per one million opportunities. A review of some basic statistics will aid in understanding of Six Sigma.

In any population there is a distribution of data. For example, consider a group of adults ranging in height from 4' 5" to 7'. The average height of an adult male is 5' 9" (CDC, 2002). Graphing this data would show a normal distribution—a bell-shaped curve. Figure 6-6 illustrates the

distribution of college male heights.

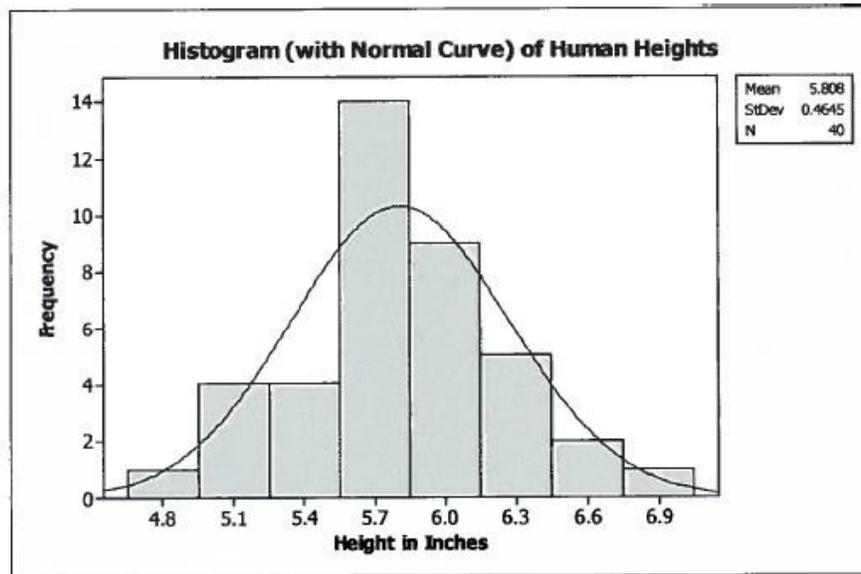


Figure 6-6. Histogram depicting distribution of adult heights

The average height of 5' 9" is located in the middle of the curve. Not everyone is 5'9", since heights vary among humans. For example, the heights of men and women are different. In the United States, the average male is 5'9", while the average female is 5'4". Differences in height are expressed statistically using the term *standard deviation*. Standard deviation is a measure of spread, or variability, of data.

In the height example, 68.2 percent of people fall within one standard deviation of the average; 95.5 percent fall within two standard deviations of the average; and 99.7 percent are within three standard deviations (Figure 6-7).

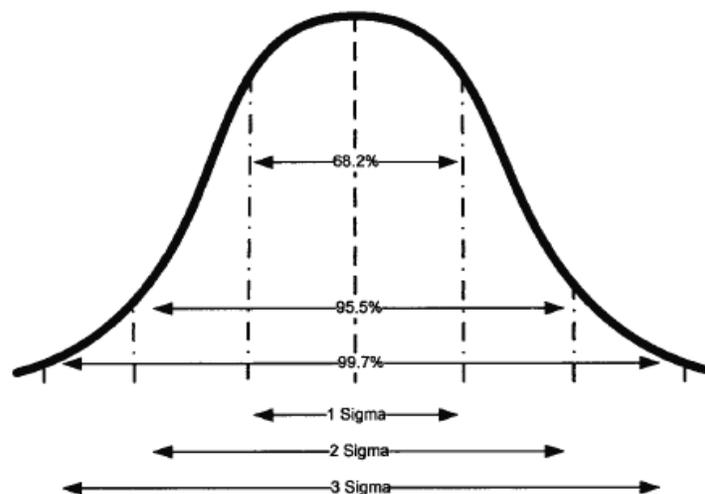


Figure 6-7. Three standard deviations, or Sigmas, of the height distribution

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## What is process variability?

Consider driving an automobile into a garage. A narrow automobile can easily fit into the space without damaging the side mirrors. In this analogy, a narrow automobile is a process that is “in control.” Slight variations in parking technique will continue to produce an acceptable level of parking quality: an undamaged automobile.

However, if a wider automobile is used (meaning a process that is less robust) and an attempt is made to park it in the same garage, there is a greater risk of hitting the side mirrors on the garage entrance. This process, while capable of achieving an acceptable outcome, is more likely to involve an accident; this is especially true if the parking process was repeated one million times. In statistical terms, the garage walls are the upper and lower specification limits for a given product. The width of the automobile is equivalent to the distribution of product quality data generated in the process. The more narrow the data spread (i.e., the width of the automobile), the easier it is to fall within specifications limits (i.e., safely within the garage walls). Figure 6-8 illustrates this. The term used for expressing how capable a process is to meet specifications is called the  $C_{pk}$  - process capability index.

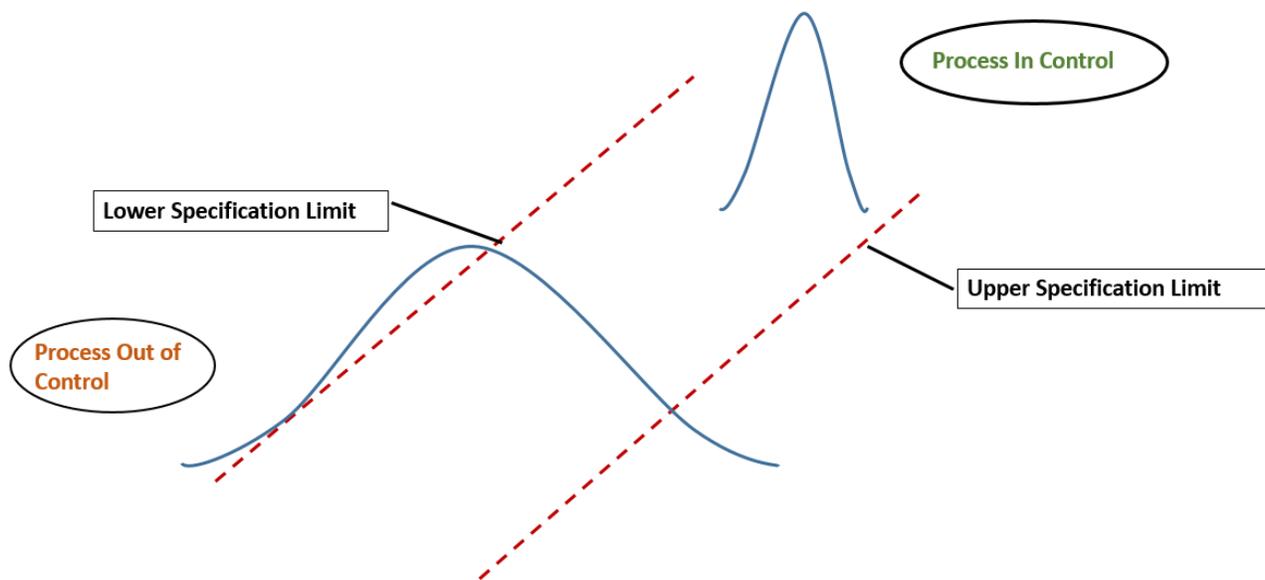


Figure 6-8. Process capability distribution depicting both out-of-control and in-control processes

Figure 6-9 is a graph depicting the frequency of maximum cell density of biomanufactured material. In this example the diagram depicts the maximum cell mass per batch during a series of *E. coli* fermentations. In the example some data points appear below the lower specification limit. This indicates the process is not capable of producing biological material within specification, so the process is out of control.

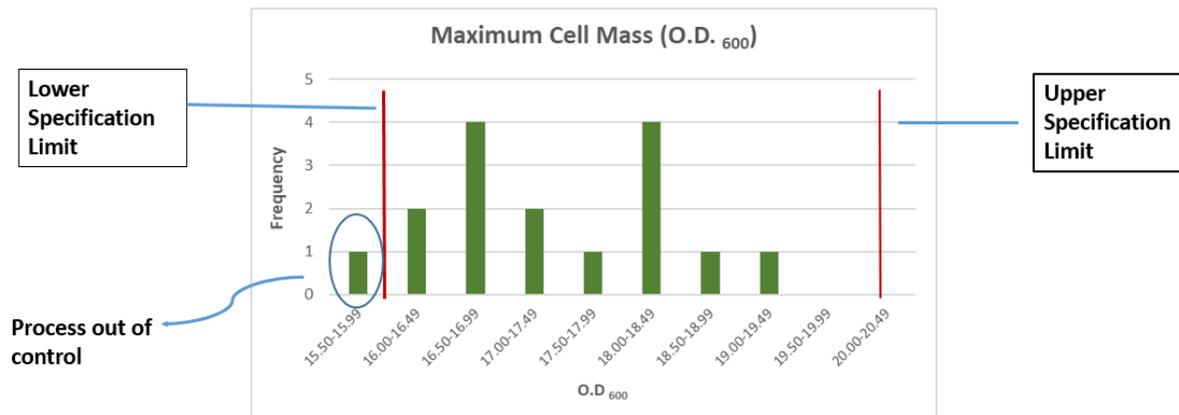


Figure 6-9. Process capability diagram depicting maximum *E. coli* cell density per batch

### How to get a process in control

What needs to be done if an 18-wheel truck needs to be a subcompact automobile? The Six Sigma improvement approach follows a five-step scientific model, referred to as DMAIC. The acronym stands for Define, Measure, Analyze, Improve, and Control. These five steps provide a useful structure for solving many complex problems.

How exactly does one go about making this evaluation and change? By following the Six Sigma process:

- **Define:** describe the problem, its effect on the business, and the improvement target
- **Measure:** determine the current process performance level; confirm what is critical to product quality and the accuracy of the measurement system
- **Analyze:** understand what is causing the problems
- **Improve:** develop a solution to the problem and confirm that the solution is successful
- **Control:** institutionalize the improvements to prevent the process from returning to its previous state

In each step of the DMAIC process, different tools are generally used; some tools, however, can be used in multiple phases. We will describe some common tools and their typical use during quality design and improvement processes.

### Define

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In this initial stage the improvement team works to clearly describe the nature of the problem. One commonly used tool to understand the current state of a process is called a flow chart, sometimes called a process flow chart. After completing the process flow chart, areas of concern become clear. This stage provides clues about the problems that might exist and where to collect more data.

### **Measure**

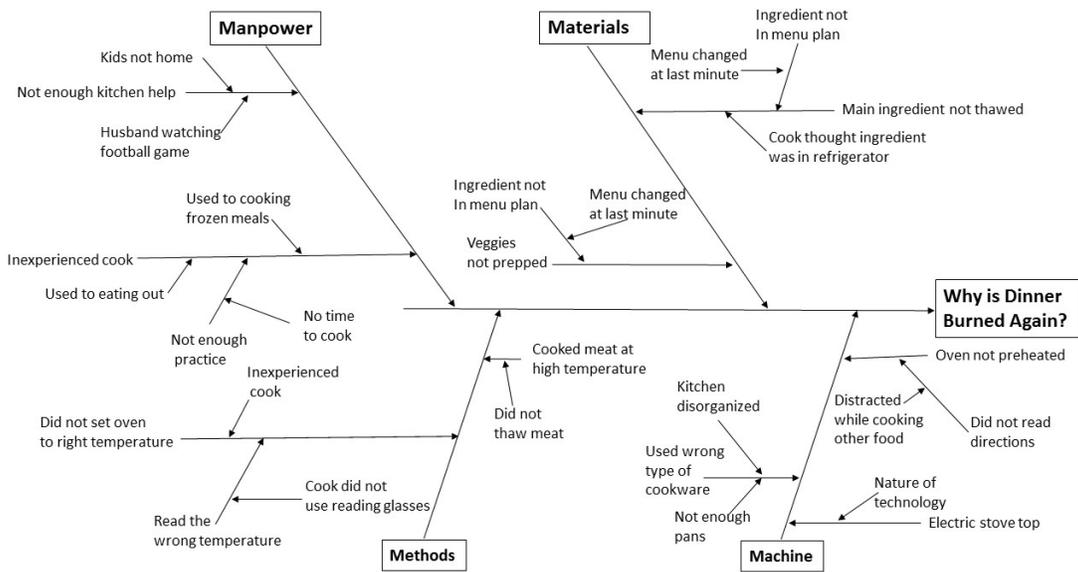
In the second stage it is important to determine what data are needed and how to collect the data. Once this is established, the actual data collection can be performed. At this point, it is important to keep in mind the problem that must be solved and what is needed from the data. For example, the time frame for a data sample may be important to consider—are data needed from the last year or just the last month? If proper sampling is not done, the problem might not be caught during the data analysis.

Key aspects of the process can be compared to see if there is any relationship (e.g., height vs. weight). To explore such parameters, all relevant sets of data need to be collected. Otherwise statistical analysis cannot be properly performed.

### **Analyze**

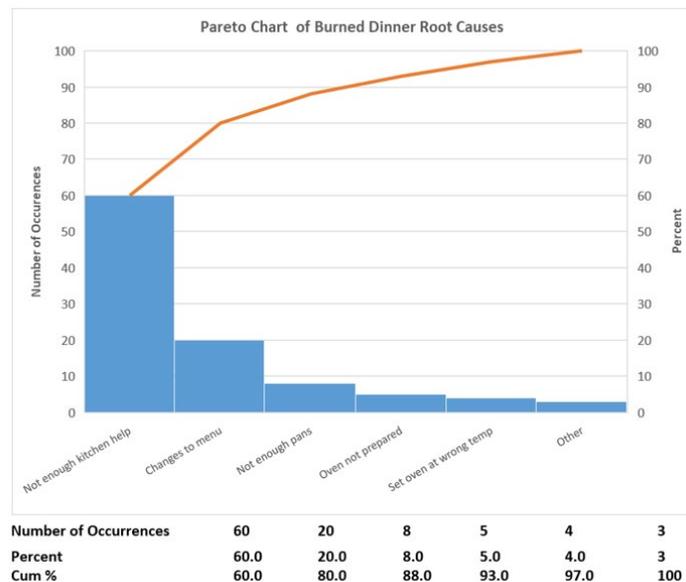
After the data are collected, the information is reviewed to determine the extent of the problem. It is during this stage that data are reviewed in earnest to determine the cause of the problem. Basic statistical analysis can be performed on the data collected, such as reviewing the maximums, minimums, and averages. Standard deviation can also be calculated to determine how much the data vary. More advanced statistical tests, such as T-tests, F-tests, and correlation analysis, can also be performed to determine which problems to solve.

A helpful tool that is often used in this stage is the fishbone diagram, also called a cause and effect or Ishikawa diagram. This is a troubleshooting tool that can be used to visually illustrate the relationship between causes and effects. Referring to the meal preparation analogy from earlier, the “head of the fish” contains the effect of a problem, such as “dinner is burned.” The major spines of the fishbone are labeled with the four most frequent causes: Manpower, Methods, Materials, and Machine. Though these are the most frequent, other categories can be used based on the nature of the problem. Figure 6-10 illustrates a completed fishbone representing the possible causes for “why dinner burned.”



**Figure 6-10. Fishbone diagram depicting possible causes for "Why Dinner Burned"**

Another powerful tool to help focus on the most important problems is a graph called the Pareto chart. Its creator, Vilfredo Pareto, was an Italian economist who concluded that 20 percent of the causes of an effect are responsible for 80 percent of the effect's manifestations. The tool is a bar chart that plots values in decreasing order of relative frequency from left to right. The graph can reveal which factors have the greatest impact and which have the least impact; this highlights areas where change will result in the most benefit (that is, to not waste time fixing things that have little impact on the process!) (Figure 6-11).



**Figure 6-11. Pareto chart depicting possible causes for "Why Dinner Burned"**

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## Improve

After completing the analysis phase and understanding the root causes of the problem, the Improve stage follows. Ideas for correcting the causes are developed and tested. One useful technique for preventing problems from reoccurring is a philosophy called *error-proofing*. In Japanese, this concept is known as **Poka Yoke**.

Error-proofing is defined as improving work operations, including materials, machines, and methods, with the aim of preventing problems due to human error. Since people are not perfect and make mistakes, the key is to improve the work operation to fit people rather than trying to make perfect humans to fit the work environment.

An everyday example of error-proofing is pictured in Figure 6-12. This device, which tethers the gas cap to the body of the vehicle, prevents the cap from being lost after filling the tank. The tether helps to reduce the probability of losing one's gas cap, as it can't be placed on the roof or trunk while fueling the car and then be forgotten.



**Figure 6-12. Example of an error-proofing device: a gas cap strap**

Mistake-proofing is often done in the original design of buildings and equipment. However, in some cases the mistake-proofing is done in response to an issue that arises after the building or equipment is in use.

The first step to devising a mistake-proof solution is to identify the reason for failure. There are five general failure mode categories, including:

- process failures: omission, excessive repetition, wrong sequence, early or late execution

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- selection failures: incorrect identification or selection, incorrect counting or calculating
  - perception failures: overlooking, misreading, misunderstanding, incorrect decision, miscommunication
  - motion failures: incorrect transcription, data entry, incorrect routing, orientation or positioning, unintentional movements
  - other failures: essential elements not available, hardware failure

Once the type of failure is identified, an appropriate intervention can be implemented for mistake-proofing.

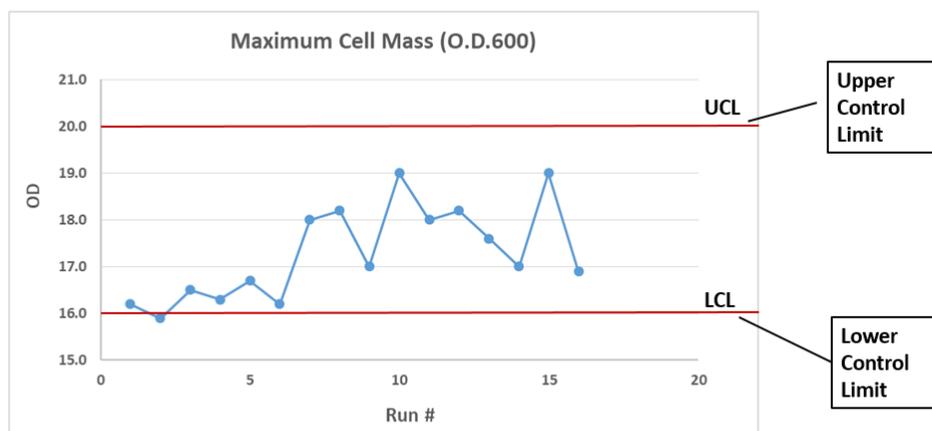
More complex problems require greater creativity in mistake-proofing or failsafing. An innovation technique used for developing error-proofing solutions is called the Theory of Inventive Problem Solving (TRIZ). The TRIZ method uses the principle of abstraction to create general solutions that can be used in different applications. Genrikh Altshuller, the inventor of the TRIZ method, studied inventive patents and categorized the reasons these inventions were successful.

The result of Altshuller's work is a list of 39 parameters and 40 inventive principles. The parameters can be analyzed using a contradiction matrix. This aids in directing the problem-solver to an abstract innovation that was successfully used for another application and can be used to solve the current problem. By looking at a proven solution, one can potentially jump to an innovative solution quickly rather than using a trial and error method. This solution-direction approach focuses the mind on a proven solution that may work well in a different setting and may help to help error-proof processes.

Before implementing error-proofed solutions, teams frequently conduct an analysis of risk prior to implementation. The tool for helping determine risk is called a Failure Modes and Effects Analysis (FMEA). Knowing if there are any risks involved in implementing a new solution is important for planning a successful implementation. If risks are low enough and the decision is made to implement, standard work practices are updated to reflect the new error-proofed, robust design. All employees must be trained on the new practices, and the new practices should be at the forefront of the training program until they become routine.

### **Control**

Updated procedures, flow charts, and training all help maintain implemented improvements during the final control phase of the DIMAC process. One tool that can be of benefit is a control chart, which is a type of Statistical Process Control (SPC) chart that shows whether a new process parameter is in-control or heading out-of-control. Control charts are graphical tools used for monitoring changes that occur within a process by distinguishing common-cause variations from special-cause variations (Figure 6-13).



**Figure 6-13. SPC for the maximum cell mass per batch for a series of *E. coli* fermentations depicting an out-of-control process**

## The Future of Operational Excellence: Deployment Challenges

The tools and methodologies of lean and Six Sigma are powerful, and the future of OE is bright. Success, however, is not guaranteed. Some organizations abandon their Lean Six Sigma efforts after only a few years. A good OE program can be successful with a strong deployment plan, continued management support, employee buy-in (i.e., taking ownership), and a change in management behavior.

Professor John Kotter of Harvard Business School found that fewer than 15 percent of organizations are successful in transforming themselves. Kotter’s popular model for leading change (from his book *Leading Change*) follows an eight-step process (Kotter, 1995):

- establish a sense of urgency to overcome complacency
- create a guiding coalition to align visible leadership support
- develop a vision and a strategy to orient people to required future change
- communicate the vision to keep it fresh in the mind of all involved
- empower employees for broad-based action by removing barriers
- generate short-term wins to reinforce the change message
- consolidate gains and produce more gains to continue the change
- anchor new approaches in the culture as evident in day-to-day work

### Creating and identifying the OE culture

Most organizations fall somewhere on Kotter’s eight-step process when establishing OE as part of its culture. The commitment and scope of involvement with OE efforts can vary for each

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organization. Some organizations focus OE efforts on the manufacturing/operations departments only, while others initiate an organization-wide effort (i.e., all functional departments use a product lifecycle approach from concept to commercialization).

Organizations have chosen different combinations of lean, Statistical Process Control, and other tools in defining their OE programs. The importance and commitment to Operational Excellence becomes apparent when it becomes part of the business fabric/culture of the organization. It is reflected:

- in communications from leadership, company newsletters, and project updates
- on signage within the organization (e.g., in hallways and offices)
- within the mission, vision, and strategic goals
- as part of the performance review process included in developmental programs for employees
- during the interview process for job openings and in orientation sessions for new employees
- in common, everyday activities (e.g., discussed over lunch) as well as the organization's events and/or celebrations

Organizations must consider their level of commitment to operational excellence along with other related issues such as:

- leadership
- skills
- training opportunities
- advancement opportunities

In today's competitive marketplace, both innovative solutions and improved operational effectiveness are the key to reducing costs and increasing profitability. New competitors continue to enter the world market and lower prices. The need for innovation, improved efficiency, and profitability is stronger than ever. Operational Excellence efforts, therefore, are a key to the long-term success of biomanufacturing organizations.

### **Lean Six Sigma credentialing process**

The OE process is dynamic and in a state of constant change, so training and credentialing programs are essential to help one gain Lean Six Sigma skills and maintain them.

#### **Individual credentials for Six Sigma**

Many higher-education institutions and private organizations offer training, coaching, and mentoring in Lean Six Sigma methods. Courses are available online and in classroom-based learning formats. Six Sigma certifications bear a naming convention similar to those found in martial arts:

- Six Sigma White Belt: awareness-level training of the basic terminology of Six Sigma and problem-solving

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- Six Sigma Yellow Belt: awareness-level training that prepares an individual to participate on an improvement team and teaches problem-solving tools at a basic level
  - Six Sigma Green Belt: operations-level training that prepares an individual to run improvement projects under the supervision of a Six Sigma Black Belt. Focuses on statistical process control and tools to identify and implement change
  - Six Sigma Black Belt: operations-level training that prepares an individual to run complex, cross-functional improvement projects, as well as coach and mentor green belts on less-complex projects
  - Six Sigma Master Black Belt: strategic-level training that prepares an individual to develop OE programs and systems, as well as coach and mentor Black Belts in running complex, cross-functional improvement projects

### **Individual credentials for lean manufacturing**

There are a few credentialing groups for lean training, most of which have a terminal certification called 'lean master'. A more advanced certification, the lean sensei, provides training in how to develop lean programs, conduct evaluations of businesses, and coach trainees.

### **Organizational credentials: the Malcolm Baldrige Award**

Named after Malcolm Baldrige, the 26<sup>th</sup> U. S. Secretary of Commerce, the Baldrige Award was started in 1987 to increase the performance of American business. The program is managed under the Commerce Department's National Institute of Standards and Technology (NIST) as the Baldrige National Quality Program (BNQP) and the Baldrige Award. The award has fostered innovation and performance enhancement across the United States as well as many other parts of the world. Over seventy-five organizations have received the award since its inception.

The categories assessed by independent examiners (with over 1,000 hours of review per company) are:

- leadership
- strategic planning
- customers and market focus
- measurement, analysis, and knowledge management
- workforce focus
- process management
- results

The BNQP's associated *Criteria for Performance Excellence* guide has over 10 million hard copies printed worldwide and has been downloaded over two million times annually. State, regional, and local accredited groups support the BNQP, and more than forty state programs are listed on the NIST website [www.nist.gov](http://www.nist.gov). Organizations undertake this program at varying rates; it can take from three to six years to achieve the award. Most organizations believe that the process itself is as valuable as receiving the award.

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## Organizational credentials: the Shingo Prize

For more than 20 years the Shingo Prize for Operational Excellence has been awarded annually to American organizations that achieve world-class manufacturing status. The prize is named in honor of Shigeo Shingo, a Japanese industrial engineer considered a world leader in improving manufacturing processes. The award is has been called, by *Business Week*, the ‘Nobel Prize for manufacturing’, recognizing lean manufacturing and operational excellence in North America.

The pursuit of the Shingo Prize is considered a transformational process for an organization, beginning with the adoption of specific tools to create solutions, followed by structuring tools into an inter-related system of improvement processes, and finally, by incorporating the lean philosophy into the culture of the organization.

- Bronze Level: at this level the candidate must complete a written exam and submit a project portfolio for review and approval, as well as appropriate tools in use and demonstrate this during a site audit by the accrediting agency.
- Silver Level: candidates must have demonstrated systems-level improvements within their work, and demonstrate this in a site audit by the accrediting agency.
- Gold Level: to achieve the highest level, candidates must demonstrate lean principles across all areas of the business and value stream, and demonstrate this in a site audit by the accrediting agency.

## ISO 9001

The International Organization for Standardization (ISO), a non-governmental organization based in Geneva, Switzerland, consists of a network of national standards institutes from countries across the world. The organization publishes a wide range of international standards for business, government, and society in general. Organizations adhere to ISO standards for various reasons (consistency across facilities/units/processes, vendor requirements, quality efforts, market advantages, efficiency improvements, requirements imposed by regulatory bodies and agencies, etc.).

ISO 9001 is a Quality Management System standard that biomanufacturers and companies engaged in all types of business can follow as part of quality and OE programs. Third-party organizations independently certify organizations for ISO 9001 compliance. The steps required to achieve ISO 9001 certified status can aid an organization in continuously improving its processes and consistently producing quality products.

Other ISO standards can benefit biomanufacturing organizations. ISO 14001 relates to environmental management systems, which can benefit an organization’s Environmental, Health, and Safety (EHS) efforts. ISO 31000 addresses risk management, which can assist organizations with economics/finances, business decisions, security, OE, and EHS.

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## Check Your Knowledge

1. Which of the following is a Japanese word that means “visual card” and describes an activity used to allow demand signals to trigger action like production or re-ordering supplies?
  - a. Andon
  - b. Heijunka
  - c. Kanban
  - d. Takt
2. There is only one way to assemble a rectangular-shaped diaphragm valve, while there is a right way and a wrong way for square diaphragm valves. Specifying the use of rectangular-shaped diaphragm valves is an example of which OE tool?
  - a. FMEA
  - b. DMAIC
  - c. Poka Yoke
  - d. Kaizen
3. Which of the following is a Japanese word that means “small changes for the better” and describes an activity used to facilitate continuous improvement?
  - a. Gemba
  - b. Heijunka
  - c. Poke Yoke
  - d. Kaizen
4. The mean of a set of normally-distributed process data should be centered at the midpoint between the upper and lower process control limits to demonstrate the process is “capable.” True False
5. A “pull system” balances the workflow and prevents bottlenecks. Which of the following is an element of a “pull system”?
  - a. increased inventory to buffer demand
  - b. segmented workplace to reduce risk
  - c. small lots to reduce batching
  - d. production speed above consumption to allow for maintenance
6. A batch record for a buffer solution directs at least 60 minutes of mixing. Mixing studies show that a buffer solution is completely mixed after 30 minutes. This process contains which type of waste? (Hint: DOWNTIME)

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7. A value stream map for a fermentation process indicates that the activities below do not add value. Which of these can NOT be reduced or eliminated?
    - a. cooling the fermentation media after sterilization
    - b. approval of the executed batch record
    - c. waiting for the harvest vessel to be cleaned
    - d. waiting for the test result before further processing

## Activities

1. Develop a Balanced Scorecard for performance measures that will assist you in achieving your career goals.
2. Sprayballs used for Clean-In-Place (CIP) operations contain an asymmetric assortment of holes so that specific parts of a process vessel are sprayed with cleaning solution. Therefore, placement of the spray ball in the correct orientation is important. Develop a way to error-proof the assembly operation.
3. Autoclave technicians prepare ten new shake flasks each week per the master schedule. The standard use rate is nine per week, thus the inventory of shake flasks grows over time. Design a Kanban system to ensure that there are enough shake flasks each week, but never more than twelve.
4. Use 5S to organize a space in your home, office, or lab. List 1-2 activities for each "S."

Form a group and discuss whether FDA approval of a biological drug product would be considered a value-added or NNVA activity.