Lean Manufacturing Applied to In-Process Protein Concentration Determination Changing the Standard UV-Spectrometer for the Solo Variable Pathlength Extinction

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Abstract

The protein concentration test is a complicated test which requires a lot of time and materials. Currently the test is being performed using an old equipment of UV-Spectrometer Visible. The goal is to implement a new methodology which can reduce both. The main objectives are to reduce the waste of the time and cost there is by using an old UV-Spectrometer. We also look for a relocation where the testing is performed to reduce the amount of time it takes to start processing the sample. By comparing the same sample in both equipment, we can calculate the average of materials and costs needed for each test. We also measured the time it takes to deliver the sample to another laboratory versus performing the test in the same room it is collected. By implementing the use of the new equipment of SOLO VPE we can reduce the time and amount of resources needed to perform the tests.

Introduction

Maintaining the workplace operating as optimal as possible we must have, and apply, the lean manufacturing methodology. In this experiment we are looking for ways to maximize the analysis of a specific sample test, protein concentration. By taking the time since the sample is taken and analyzed, we can calculate an average amount of the total time it takes to perform it. By eliminating the routes, the sample needs to go through we expect a reduction in time. It is also important to stay up to date with the current technology, which is why we compared the current UV-Spectrometer used for the test with a new equipment, the SOLO VPE. We will compare the amount and price of materials used per equipment in order to justify the use of the new equipment, but staying within the established parameters of the tests.

Background

Henry Ford was the first one to start revolutionizing how to improve an automobile assembly line, but was limited to a specific model. Then Taiichi Ohno and Kiichiro Toyoda improved his way of thinking to improve the flow and variety. Lean methodology was born, it can be defined as the ability to eliminate waste in order to make a process achieve a continuous flow [1]. Inside lean manufacturing there are techniques like 5s and Six Sigma where the flow can be observed and measured. To make organizations more efficient they must eliminate non-value added activities to reduce waste and costs, they achieved their goal by applying Sig Sigma [2], Operational Excellence and Kaizen techniques which helps them standardize the work. Some ways to eliminate waste can be lowering the number of defective units, over-processing, motion, overproduction, waiting time, transportation and inventory space. By measuring, with different metrics, them with a before and after we can quantitively see the amount of time and money that can be saved and used for other tasks.

Business also use the product lifecycle management approach which helps them reduce costs, improve quality and innovate products. It is important to identify which activities are the ones that add value in order to create a value stream map. This helps maintain a constant flow of work and reduce waiting times [3]. Visual aid in the processes helps the employees have a better understanding of what should be done, how and how fast. To achieve a lean process, we can use as many tools as we can, including the steps from DMAIC, which are define, measure, analyze, improve and control.

There are many types of UV-Spectrometer one is the 60-beam OMEGA laser system which is used for inertial confinement fusion studies. It has 60 different configurations that consist in a main infrared beam of pathlength of 1053nm that passes, and amplifies, through a Potassium Dihydride Phosphite crystal and produces a UV light of 351nm [4]. The Omega UV is a complicated equipment which uses multiples crystals to change the bandwidths when applying the spectral dispersion. Is a technique to produce a more uniform and time integrated illumination profile at the target. There are many variables which can affect the measure of the beam, one is a change in the intensity in a rapid variation in time. It is a complicated equipment compared to our UV-Spectrometer.

Every equipment requires instrumental calibration and verification in order to get the desired results, but they are subject to errors. Any laboratory that performs tests, and provides to the United States, is ruled by stipulated standards. In the US it is under the cGMP's regulations. The United States Pharmacopeia General Chapter on Analytical Instrument Qualification became effective in August 2008 [5]. It stipulates that all instruments need to be calibrated, have established written directions, schedules, limits of acceptance criteria and steps to perform if there is an out of limit result. The definition of calibration is the set of operations which established the relationship between values indicated by a measuring instrument and the known values of a reference standard. The absorbance is verified by using a Certified Reference Material with a known concentration. A mean value is calculated and compared with the one of the Certificate of analysis.

There is a new equipment for protein concentration which requires less materials, and takes less time. The Solo Variable Pathlength Extinction (Solo VPE) [6]. Slope Spectroscopy leverages the power and flexibility of variable pathlength technology to create a rapid, robust, and repeatable concentration measurement method for biologics, small molecules, or any sample typically analyzed with UV-Vis methods. Unlike the single value dependence of legacy UV-Vis methods, the data dense slope method characterizes samples by collecting multiple absorbance data points at several pathlengths to create a section curve (Absorbance vs. Pathlength plot) [7]. Even though the Solo VPE equipment can acquire data from the traditional UV-Vis method, the main methodology is using different pathlengths which are dynamically controlled. The sample using the Solo VPE used was Myoglobin, were different pathlengths were measured and with the Beer-Lamber Law we can demonstrate that the pathlength is directly proportional to the absorbance. With a specific wavelength we can measure both values and generate a graph, which we can calculate with a linear regression[8]. The range which we use the Spectrometer is in the ultraviolet, visible and near-infrared regions. In comparison, there is another method used for more complicated solutions or materials, it gathers reflected light. It is called diffuse reflectance spectroscopy (DRS), it provides direct information about chemical nature and is a quantitative. It has an advantage, it can be used were the material is and there is no need to get it to a laboratory [9].

Problem

After many years of performing an analytical testing for the in-process protein concentration using an Ultra Violet Spectrometer, the laboratory analysts noticed that the procedure and equipment were really time, and material, consuming. The downtime increases because of the different stages it has to go through. The sample is collected in the manufacturing area, delivered to the laboratory, the test is performed, the results are calculated and then sent back to the manufacturing area. Most of the time the personal from manufacturing area has everything set up and there are not many tasks they can perform while they wait for the results. On the other hand, the laboratory has to perform a serious of critical steps to process the drug in order to get the desired results. Since it has many steps, there is a great chance to commit a mistake, which can lead to a re-test and more downtime hours and more use of materials. This increases the cost of the test which is not a desired outcome. The equipment of UV spectrometer is outdated, has a complicated methodology, requires buffer preparation and uses a lot of materials. Any minimum alteration in the quartz cuvette, like a scratch or residue, can change the value causing the test to fail. This has a high change of human error since there has to be at least a minimum of three measurements per solution used.

Methodology

To start we needed to find the procedures and parameters approved by the FDA and the USP. After that research is done, first we need to perform the usual test with each of the steps starting from the time the sample is collected from the manufacturing tank. The next step is to start measuring the time it takes to get to the laboratory. We need to perform an analysis on the amount of materials used to perform the test, the amount of money they cost and the amount of time from start to finish of the analysis. This will give us an accurate idea on what the total cost and time is. We need to validate the Solo VPE equipment to analyze the current protein sample we need. After that we repeat the same analysis of cost of materials and the time of the testing, and the time it takes to get where it is performed. We can proceed to the next step which is the comparison between both results of each equipment. The Solo VPE will be installed in the same manufacturing are which the drug is collected. The personal will require training.

After we perform and compare, the performance of each equipment, we could average the production lots made per week, monthly or yearly. This can show us the amount of time and money saved on a yearly basis. The data should be presented in tables and graphs for a clear representation of the result. This can be the first milestone.

The next phase should in clude the specific steps on what should be the implementation of the equipment inside the area, implement the new methodology and change the SOP's. We must first validate the new methodology that will comply with the parameters and the results should be the same of with the other equipment. The test will be done and evaluate like before in order to evaluate the integrity of the testing. The new parameters, once verified and checked, can be implemented to the SOP's using a validation process. This can take at least two or three months since is a change can impacts a lot of the manufacturing and quality process. We have achieved another important milestone in this part.

We need to justify the movement of equipment from one area to another. To achieve this, we need to collect numerical data and statistics of time. We proceed to do a weekly monitoring of the time the sample is collected until it arrives at the laboratory. We present this to both areas in order to have access to the workflow of both. With a calibrated stopwatch we proceed to enter the manufacturing area before the sample collection, this is time 0. When they connect the needed equipment to collect it is when we start to time it. We follow the operator through all of the stages he goes through in order to get to the laboratory. We also collect the number of steps as another measure of comparison. The stopwatch is never stopped, but we need to document the stages the sample goes through. The first data collection since the sample is collected in when is set on a material exit airlock. After this we need to stay with the operator, the amount of time the sample is on that airlock is the amount of time it takes the operator to get undress and out of that area. This time is also annotated. Once he picks it up again, it needs to be transported to another airlock, the time and steps are written down. Again, the amount of time of the sample spent on that airlock is the amount of time it takes the operator to change clothes again and picks up the sample. The number of steps is recorded and the time also. The sample is picked up and transported to the laboratory where it is documented as delivered, and put in a refrigerator. We can perform a calculation to change the number of steps into distance of feet using the equivalence that 1 step is 2.5 feet. These two measurements were performed only one time since the route taken is always the same. After this, we can designate an area, where the sample is collected, for the use of the protein concentration equipment. We proceed to evaluate using the same criteria, time and distance.

The next part is to achieve the justification of the use for the new equipment to process the sample. We need to do a comparison of the use of materials of the UV-Spectrometer for a sample and the same for the Solo VPE. We proceed to perform the protein concentration test on the UV equipment. We decide to test 3 samples to calculate an average of material used per sample. We also estimated and overall value of all the materials used per equipment. We made a list of each of the individual material that needed to be used in order to complete the test following the procedures. The sampling was performed on different days because the analysis takes a lot of time. On the first day we calculated and average of the materials used for that sample, from beginning to end. This step was repeated 2 more times for a total of 3 samples. For the SOLO VPE we also analyzed 3 samples on 3 different days, writing down each of the materials used to calculate an average cost per sample. On this stage every single material used is documented and assigned an individual value. The total cost of each of the equipment is compared and analyzed to have an overall idea of the difference in cost (Figure 1). In order to be more specific, we calculated the individual cost of each sample and calculated and average for each equipment (Figure 2). Another data that was gathered during this process is the amount of time it takes to perform the test since the delivery of the sample to the designated area. Here we just calculate the time since the analyst took the sample and the end time when the results are sent to the specific area.

Results and Discussion

The first part is the time evaluation it takes to perform the sample test in the laboratory using the UV-spectrometer and compare it to the time it takes to perform the test inside the area where the sample is collected. The measuring of time starts since the sample is collected in the manufacturing area (See table 1). The sample has to go through different airlocks in order to get them out of the area, and it also includes a change of clothes from the operator. After it arrives on the laboratory the analyst must perform a serious of steps prior the start of the testing in order to analyze it. The amount of time it takes to analyze the sample since the time of collection is about 270 minutes, in comparison with 120 minutes (table 2). This measurement does not include the time it takes if the sample fails the test and it has to be repeated if the test was performed with the new equipment inside the area where it is collected. When analyzing and applying the lean manufacturing mentality and techniques, we can see that there is a waste of time of 150 minutes. This is more than 2 hours that any employee can use to perform other tasks.

This brings us to the next part of the evaluation, cost. If we compare the total costs from both equipment (table 6), even the first investment from using the UV-spectrometer is higher than the SOLO VPE. From a clear view we can see that the SOLO VPE uses less materials, which involves also less inventory space. Since we needed a more specific comparison, 3 samples of each equipment were tested and measured. Each sample per equipment was prepared in the same way according to the methodology. After we calculated an average cost per sample for each test. In this part we performed a hypothesis test to help us prove that the use of the new equipment, SOLO VPE, would have a lower cost per test than the old equipment, UV-VIS Spectrometer, see Table 7.

After the approval of the new equipment there are a serious of tests that needs to be done prior to use. It requires a validation process for the new methodology. The results must be specific and there should be no interference from the new materials and mechanisms with the determination of the protein. This can be done by taking measures with empty plastic cuvettes and fall inside the parameters. The results must be linear, directly proportional to the concentration of the sample. It can be by measuring multiple samples of different concentrations. We need to perform a test to see how accurate the sample is to the expected value. The equipment precision can be evaluated by measuring different samples from the same analyst in order to see the repeatability, or from different analysts to see the reproducibility. A system suitability test is also performed before the samples and after the samples to ensure that the equipment is working as expected. The value given should be within parameters of the reference material with a given COA.

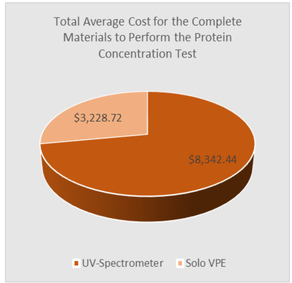

Figure 1
Visual Total Cost Comparison

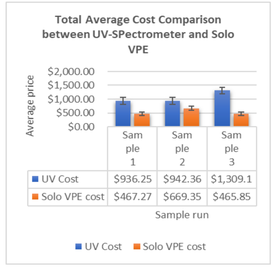

Figure 2
Total Average Cost Comparison Between UV-Spectrometer and Solo VPE

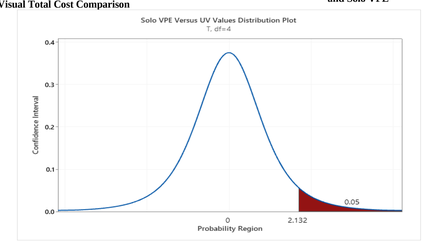

Figure 3
T-test of Two Sample Assuming Unequal Variances

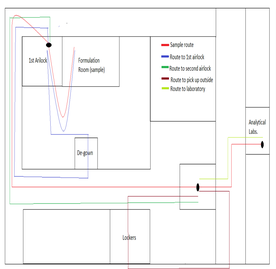

Figure 4
Spaghetti Diagram of Route of Sample and Operator Before the Equipment Implementation

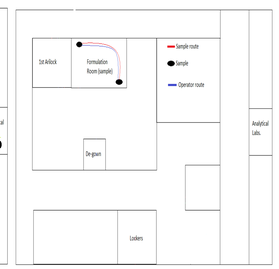

Figure 5
Spaghetti Diagram of Route of Sample and Operator After the Equipment Implementation

Conclusions

After applying the Lean Manufacturing techniques to the whole process of the analysis of protein concentration there were a lot of areas of opportunities which were improved. By analyzing the work flow and steps that the test had to undergo, using the UV-Spectrometer, we gathered a great amount of information that helped us make changes. The overall amount of time saved by changing the test from one area to the same area which it is collected was substantial. By eliminating the different pathways which the sample had to go through we have increase the speed which the test is started and performed, and there is more time for the analytical analyst to perform other tests. By capacitating the manufacturing employees to perform the test in the same area we also avoid having downtime of waiting on the sample results.

Although a lot of time is saved by moving the equipment from the laboratory to the sampling area, we can also see a time and cost reduction by implementing a new equipment to perform the test. The use of SOLO VPE significantly reduced the cost of the test and reduced the overall testing time. By comparing the material cost of each equipment, it components, and amounts of raw material needed per sample, we can see the average saved using the new equipment. The UV-Spectrometer requires a lot of maintenance, a great amount of materials, and has a higher chance of error. This is because with the new equipment we eliminate the need to prepare, and use, a buffer solution to get the readings. The SOLO VPE doesn't need the preparation of a buffer solution, and the sample can be dispensed directly.

Future Work

With the acquired results we can demonstrate that getting a new equipment to perform the mentioned test, improves in many ways the process and we can apply this information to the other areas that also need to perform this test. We are looking forward as a first step to relocate the protein concentration equipment into the manufacturing area and give the adequate training to the employees. The gathered data could be expanded with more runs, to have a bigger pool to compare from. Finally, we expect to promote the lean manufacturing methodology via training so anyone can present areas of improvements, or opportunities, and present them as future projects. To standardize all methodology in every department that perform this test.

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