Quality System Management for Process Analytical Technology Applications

Deborah E. Nieves Mercado
Manufacturing Engineering
Edgar Torres, PhD
Industrial Engineering Department
Polytechnic University of Puerto Rico

Abstract *— Commonly the pharmaceutical industry uses a system known as the traditional or conventional process for the manufacturing of their products. Now, it has been shown that the use of other systems not only benefits in product quality, but also on cost-effective and process efficiency. This is why the Food and Drug Administration has initiated a revolutionary campaign to encourage the industry on implementing new system upgrades. Process Analytical Technology or PAT is a set of tools that will provide with better understanding and control of the process. Some of the benefits provided by the technology revolve in the reduction of production costs by reducing cycle-time and the overhauling of the process for making it more eco-friendly. Both techniques have unique characteristics, but is important to highlight this improvements to the manufacturing process in order to provide us with high quality products in our quest for better quality of life.*

Key Terms *— Analytical Process, Food and Drug Administration, Process Analytical Technology, Traditional Pharmaceutical Manufacturing Process.*

INTRODUCTION

During the last century, pharmaceutical manufacturing has provide the world with a wide variety of vanguard products that has helped-us and still helping to this day, overcome many health related issues and has improved our overall quality of living. These products are being manufactured by implementing a system known as Conventional or Traditional Pharmaceutical Manufacturing Process.

Although the pharmaceutical industry is providing the market with enough products, this system is not efficient and cost-effective enough that create considerable financial losses and in some cases, poor quality products. Long validation steps and extensive testing procedure are some of the futures that characterize this process. In general, this process operates batch processing with laboratory testing on collected samples to evaluate and ensure the quality of the product [1]. It analyzes a random sample of the batch at the end of its production, making it difficult to know if the product meets the correct requirements before the final batch is finished. If the sample does not meet the expected quality requirements the complete batch is discarded. On the other hand, if the sample meets the minimum quality criteria set by the manufacturer, the product is released.

Because it is the manufacturer who sets the parameters, requirements could be set low enough as seen fit to not loose profit. These low parameters may increase the probability for this released batch to be recalled from the market, creating the problem of not only loosing money, as mention above, but also releasing to the public batches of products with unknown quality that, at worst, could cause harm to its user, aggravating not only the industries economic loses but its reputation too. To overcome this type of uncertainty, today, significant opportunities exist that improves the efficiency of the manufacturing process and assures quality through the innovative application of novel products and process development, process control and modern process analytical chemistry tools [2].

The United States Food and Drug Administration (FDA) have initiated a revolutionary campaign to encourage the pharmaceutical industry to implement new processes with a more systematic approach. One of these processes is a new way of operation known as Process Analytical Technology (PAT).

PAT is a system for designing, analyzing and controlling manufacturing through timely measurements (i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes with the goal of ensuring final product quality [3]. The purpose of PAT is to deliver high quality products by incorporating an efficient, cost-effective analyzing technique to the manufacturing process. To do so, it is important to take full advantage of this technique by applying it during the products' research and development phase. Doing so, high quality parameters will be measured and analyzed from the very beginning of the products' production process resulting in high quality products with a simple, effective and successful manufacturing process.

This technology will be bringing great benefits to the pharmaceutical companies who implement it. Some of these benefits are:

- Decreased in cycle time
- Higher final product quality
- Increased production efficiency
- Better process capacity
- Decreased operating cost
- Fewer rejects

PAT consists in the use of various tools to ensure the quality of the products therefore increasing efficiency and cost-effectiveness.

PAT TOOLS

Process Analytical Technology or PAT, delivers a set of new tools as well as current ones that will provide with valuable information and understanding about the process, giving more inside about the scientific, risk-management pharmaceutical development, manufacture, and quality assurance of the system [1]. These tools can be categorized according to the following points:

- Multivariate Analysis
- Testing and Analysis
- Control Tool
- Continuous Improvement

Multivariate Analysis

Some of the development strategies used to identify optimal formulation and process, are the bases for the product and process design, making them a complex multi-factorial system if we look at it from a physical, chemical and biological perspective. This tool is based on the statistical principle of multivariate, which means that these tools will be analyzing more than one variable at a time. Statistical design of experiments, response surface methodologies, process simulation and pattern recognition tools are some of the multivariate mathematical approaches.

The statistical principle of orthogonally and randomization are the best of the methodological experiments. These experiments would study and identify the effect and interactions of product and process variables. These tools enable the identification and evaluation of product and process variables that may be critical to product quality and performance. Also, is able to find potential failure modes and mechanisms and qualify their effects in product quality [1].

Testing and Analysis

For years, the analysis of the processes has gone through significant improvements seen reflected in a new ways of collecting data from the process it self. Sophisticated measurements tools that give the chemical composition and physical attributes have replaced the conventional tools that were used. These tools provide nondestructive measurements that contain information related to chemical and physical attributes of the material being processed [2]. The measurements are divided in three types of testing:

- At-Line Testing
- On-Line Testing
- In-Line Testing

For the AT-LINE TESTING the sample is removed and tested near the process stream. In the ON-LINE TESTING, the sample is taken from the process to measurements using an analytical chemistry approach and can be returned after. For the IN-LINE TESTING the measurements is made in real time and can be in an invasive or non-

invasive way. In this test the sample in not removed from the line and uses place probes that are in constant contact with the product samples.

These tools provide with better control of the process and the technology used for this testing is very sophisticated. This technology is able to analyze the sample without destroying or reacting with it. Some of these physicochemical techniques are: Near Infrared (NIR), Raman, Mid-Infrared (Mid-IR) and acoustic emission signals. We can apply these non-traditional techniques in the areas of drying, assay, blending and content uniformity. Taking for example the NIR, some of the benefits that this technique provide for on/in-line testing are:

- No waste
- Need some or no sample preparation
- Does not require the use of solvents
- Process needs little monitoring
- Measure both properties: chemical and physical

This technique would provide real time information improving the quality of the product and lowering the production cost.

Control Tools

An essential role of the pharmaceutical manufacturing process is to maintain control over the process. To achieve this control, the development of a good control strategy and continuous monitoring is necessary. A control strategy would help us manipulate the parameters to maintain the desire state, moreover ensures us that the quality of the output material and the final product is consistent. Guarantee and an effective control of all critical quality attributes are essential. To achieve this, is necessary to understand the close link between the product design and process development. Within the PAT framework we can include the following steps for the design and optimization of the manufacturing processes:

- Identify and measure critical material and process attributes relating to product quality.
- Design a process measurements system to allow real time or near-real time monitoring of all critical attributes.
- Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes.

With the application of PAT to the process, the fraction of the in-process materials and finished product, when evaluating, will be grater than the currently used in laboratory test. By having a wider population fraction, PAT provides us the option of using rigorous statistical principles. With these principles we can define the acceptance criteria for end-point attributes. PAT assures high quality in every batch, and provides detailed product information, making it easy for us to understand.

Continuous Improvement

Analyzing and understanding the products' production cycle is very important. The data collected from this analysis will give valuable insight and knowledge to the manufacturers. It will provide them with sufficient decision-making information so they can introduce changes and/or improvements, or the addition of new technology to the system. This will render a cost-effective and efficient production process, the delivery of great quality products and facilitating data transfer and communications with the regulatory agencies. To have continuous improvement is important to search for new tools and technology wile maintaining constant upgrades to the system. With these improvements, the manufacturing processes will deliver high quality products and reducing, at the same time, the binding fate of the system on becoming obsolete.

Risk-Based, Integrate System and Real Time Release

In a quality system, its important to keep in minds the risks of producing bad quality products. It is necessary to understand every part of the process, by doing so changes or modifications to the process can be made with less regulation. On the contrary if a process is not well understood, regulations tend be more strict making it more difficult to introduce changes or modifications to

the system. Focusing on understanding and getting to know well the process can facilitate regulation decision-making based on risk and innovation. With PAT, in order to run a process free of risk and within first-rate parameters of pharmaceutical manufacturing, it is important to keep in mind a few key points: the incorporation of the latest concepts focused in risk management and quality system; make sure there is coordination between inspection processes; and the implementation and promotion of the use of resources in an effective way to deal with the most significant health risks.

This changed regulatory environment increasingly demands that the risks are mitigated by powerful control solutions that react to the data and implement the necessary feedback control; proactively enforce best practices, quality, and regulatory compliance while helping avoid the risk, costs and time delays of waste and errors; and most importantly, monitor all aspects of the system. [4] Simplifying security problems during production stages is necessary to comply with good manufacturing practices. To achieve this is necessary to combine all the information that can control and follow each aspect of the development of the product life cycle and integrate it in a designated place.

According to the FDA real time release testing (RTRT) has the ability to evaluate and ensure the quality of in-process and/or final product based on process data [1]. RTRT come with many benefits and some of this are: that the risk of losing batches can be reducing because of the continuous monitoring and the variability in raw and in-process materials can be adjusted. Also the RTRT supply important information and understanding of the process to have control over it. Finally the quality of the end product can be measured during the production process. With the RTRT the end product testing can be replace, but not the review and quality control steps for the released batches.

QUALITY SYSTEM MANAGEMENTS

Quality System Managements (QMS) porpoise is to eliminate by validation parameters, rules and expectations that are not in conformity with the clients. This is why is important to comply with all parameters stipulated beforehand in order to manufacture high quality products. With this validating system every step of the process is being controlled and can be manipulated to assure that the final product obey all quality requirements. Because most of the validating is done during the Products' Life Cycle, this cycle has a very important roll in the validating process, so understanding this cycle is key. The product life cycle can be divided in five stages: Design, Manufacturing, Distribution, Customer and End of Life, as shown in Figure 1. Knowing and understanding the life cycle of the product, the following can be achieved; reduction of market time, quality improvements, cost reduction, identify new sales opportunities and reduce environmental impact at the end-of-life stage of the cycle. It is of upmost important to know and understand the life cycle of the product to maintain a controlled process that comply with quality requirements. The information and knowledge acquired during the development of the process are key pieces for a successful validation.

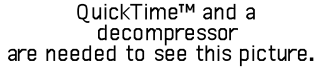

Figure 1
Product Life Cycle

COMPARATIVE ANALYSIS OF PAT PROCESS VS. CONSERVATIVE TRADITIONAL PROCESS

The role of today's analytical techniques is the same as the ones used before. They consist in testing the quality of the intermediate and final products for the sole purpose of providing feedback to the operators for quality assurance, as shown in Figure 2. Some of the tests still used today are HPLC and GC for quality parameters measurements. For example, HPLC is employed for analyzing potency, content uniformity, chromatographic purity and drug release profiles; all of these parameters are used for quality evaluation of the product [5]. Contrary to the traditional technique, PAT uses a precise sophisticated analytical system producing a higher quality product by examining the sample in real time. Instead, as seen in Figure 2, batch process analyses sample only at the end of each stage. PAT uses highly sophisticated software and hardware, which receives feedback from different stages, preventing the process from being disrupted thus maintaining full control over it as shown in Figure 3. For reasons already mentioned, PAT is considered the new manufacturing technique of the 21st century.

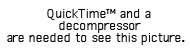

Figure 2
Overview of Traditional System Analytical Process

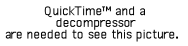

Figure 3
Overview of an Analytical System Implementing PAT

Both techniques have characteristics that are advantageous for some pharmaceutical manufactures. For example, the traditional process is beneficial for small business that cannot afford a continuous production. Also this technique is extremely popular with companies that perform trial test, because if the lot is not sold or is of no interest, production is terminated with no significant losses. Other advantage offered by this technique, is that it is useful for processes that manufacture seasonal items, products with difficult demand prediction and products that have a high difference between production and sales cost.

With PAT, we can find that one of the most important advantages is the quality of the final product. The process is continuously monitored, avoiding waste, rejects and reprocessing. Also the process is automated, which brings to the operator safety and prevent human errors. When we understand and have complete control of our process, we can detect problems and adjust the process to make it more green. This is another huge benefit that we can find using PAT; it completely transforms the process making it more eco-friendly, for instance, the energy consume by the process during drying stage of production could be reduced by 80% [6].

Both processes bring with them economic benefits. The traditional process reduces the initial capital investment using a single production line to manufacture more products, since it is more const-efficient to produce a certain number of each

element in a single run. PAT helps reduce production costs with automation and elimination of unnecessary work like the start-up and shutdown of large volume productions, reducing the production cycle time.

As in any productions, is necessary to take into consideration the disadvantages that come with each technique in deciding which process to use. One drawback found in the traditional process is the lack of flexibility that this production technique has, since it is difficult to make fast enough alterations to the system when complications arise. In comparison with PAT, the operator receives feedback to fix any problem before the final product is completed. Another disadvantage is the loss of time and effort each time a new batch is to be produced. Each time, the equipment must be stopped, reconfigured with the appropriate parameters and tested. This lengthens the time of production and reduces cost-effectiveness adding losses to the system. Finally the use of this technique results in the accumulation of incomplete lots, since the first phase of production is already completed, stocks of incomplete productions build up, waiting in turn for the next phase. This brings great economic losses, as it will not only require more storage space but also increases the possibility of losing the incomplete batch by damage of either external or internal factors. In PAT the implementation of this system needs a substantial investment for its design and complex machinery, which can be considered a disadvantage for small business. Another disadvantage is the application of the technique, as it is recommended for use only in process that is their development stage. Applying this technique to a process that has its products in the market could bring different results causing the product to be returned. The only way to apply PAT to an old process is in the cases where the product has been returned, because, then, a new process can be develop implementing PAT.

DISCUSSION

Even though the traditional process provide some advantages depending on the companies' needs, some which were explored in the analysis segment of this article, the upgrades that PAT brings to the system delivers a more innovative approach to a systematic production process that in my opinion, is preferable and it should also be to the industry. The vanguard technology implemented by applying PAT lays out the appropriate tools that tell the complete history of the finished product by yielding great insight and specifics of the evolution of the chemical, physical and/or biological changes the substrates go through, until developing into a high quality product. On the other hand, with the traditional systems, this entire information gathering is close to impossible to obtain, but PAT bridges that gap to the unknown by providing all that important information by round-the-clock monitoring and constant feedbacks by the equipment and at the same time making its difficult to the system to not meet the parameters and delivering a bad quality product. The pharmaceutical companies that opt to implement PAT in their systems, will experience what it is to have complete control over the process and the precise prediction of the dissolution results will be possible even when the final product hasn't yet been analyzed. PAT is the technology that will launch the pharmaceutical industry into an innovative future in where pharmacological products will be of great quality for the welfare of the public.

SUMMARY

Based on studies made on the different techniques, the old and the new, used in the manufacturing process, this article is intended to present with a simple yet informative analysis, that focuses on the traditional and still used system and the new tools that are available now like PAT. The analysis presented in this article emphasizes on the benefits that these new technologies brings, not only to the industry's finances, a very important

factor with strong influences on decision-making, but also, and more importantly, better high quality products. These new technologies and their applications, results in a marked overhaul that will have a great impact on the industry by challenging the companies status-quo, and basically implementing a needed change on how things are done, creating a new, more efficient, clean, controllable, cost-effective, production process that above all, yields quality.

CONCLUSION

Both techniques have unique characteristics, but is important to highlight the importance of improvement of the manufacturing process to provide the public with high quality products in our quest for better quality of life and health. One of the most important aspects of PAT is that it bring to the company valuable information obtained from the process it self, by using advanced technology that will give us the knowledge and valuable insight to take full control of our process. It also gives us the necessary information to understand the characteristics of the raw materials and manufacturing parameters, that will help us predict the outcomes of complete process, will provide with a robust process, high quality product, control over the system and the reduction of production time creating a considerable amount of saving for the manufacturer and the public.

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