Review Article

Risk Assessment in Pharmaceutical Industry - Using PAT

Sandhya K, *Gangadharappa H.V, Kiran H.C, Rasika Patil
Department of Pharmaceutics, JSS College of Pharmacy, JSS University, Sri Shivarathreeshwara Nagara, Mysore, Karnataka, India.
***Corresponding author's E-mail:** gangujss@gmail.com

Accepted on: 30-01-2016; **Finalized on:** 29-02-2016.

ABSTRACT

PAT (Process Analytical Technology) is a technology which analyses critical quality attributes with an aim to build quality for the finished product by decreasing the risks and errors. PAT is a new technology providing chance to manufacturers for the monitoring, maintenance and production of better quality products and even advancement in pharmaceutical field to check the product quality by means of chemical, physical properties including inline, at line and off line checks. Risk assessment is also equally important with the implementation of PAT. A very good understanding of manufacturing process and innovative technologies are required to prevent the problems or risks which will occur in pharmaceutical industries. Reducing risk by assessing it during manufacturing process plays important role which assures the quality and product standards if it is involved with proper principles, methods and tools. The inclusive process analytical technology projects proper process analysis, understanding, control and risk based management within FDA (Food and drug administration) regulations. The genuine concept targets for understanding the processes by defining critical control parameters and monitoring them by risk assessment in a timely manner, thus being more efficient in testing while at the same time reducing over processing, enhancing consistency and minimizes rejects. Over all process analytical technology provides basis for to produce adequate quality product which satisfies the needs of customer and provides a challenge for the organization. It ensures building of quality inside the product than the quality product which also provides great level of confidence and assurance of quality for the manufactured product.

Keywords: Risk assessment, Quality, Critical control parameters.

INTRODUCTION

Process analytical technology (PAT) is a designing, analyzing and controlling manufacturing process through timely management during processing with the goal of ensuring final product quality including raw materials and in process materials. Process analytical technology is a revolution in the pharmaceutical industry initiated by USFDA to reduce the risk of making poor quality product and involves continuous process improvement, chemical, physical, microbiological and risk analysis conducted in an integrated manner[1]. PAT is a real time testing which involves the understanding of processes and components/variables those are affecting final product. It intern indicates that quality is build into the product but not tested in the final product. The factors involved with PAT is given in Fig.1

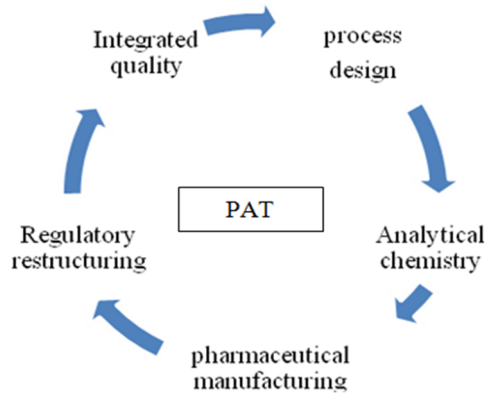

Figure 1: Factors involved with PAT

History[2], Business view[3] and regulatory view of Process Analytical Technology (PAT)[4]

History

To address the quality control problems and there by ensure the best medicinal products for the US citizens, the FDA assembled a subcommittee in 2001 to establish guidelines for the use of quality testing methods that is called Process Analytical Technologies (PAT's). In August 2003 the FDA issued a draft guidelines for the implementation of PAT, which suggests "will encourage the voluntary development and implementation of innovative pharmaceutical manufacturing and quality assurance". Unfortunately, the conventional pharmaceutical manufacturing procedures are treated as being frozen at time of conducting phase –II clinical trials. With this outlined regulatory framework, FDA tries to motivate the pharmaceutical industries to improve the production process. Generally, the PAT initiative from FDA is only one topic within the broader initiative of "pharmaceutical cGMPs for the 21st century- a risk based approach".

Business view

The pharma with its paper-based control systems PAT is different technology, but it is old that to industries such as food and beverage, petrochemicals and semiconductors etc. US drug companies had the ability to use process control for 20 years, but they have not used it because it is more expensive in term of the cost of the equipment, the cost to develop qualification, validation

and quality systems. There are no industry leaders yet demonstrating the value of PAT, so pharmaceutical companies are approaching PAT with uncertainty. The business benefits of PAT is given in figure 2. Although PAT increases the production efficiency and rate, this may not be viewed from a business standpoint as a strong impetus for change due to the perception that the implementation costs may outweigh the return on the investment in various cases, especially for small pharmaceutical companies which manufacturing drug product and dosage forms that are already struggling with tight or nonexistent margins. With limited available capital, equipment, and talented human assets, maximizing asset utilization and return on assets is becoming vital to future success and survival.

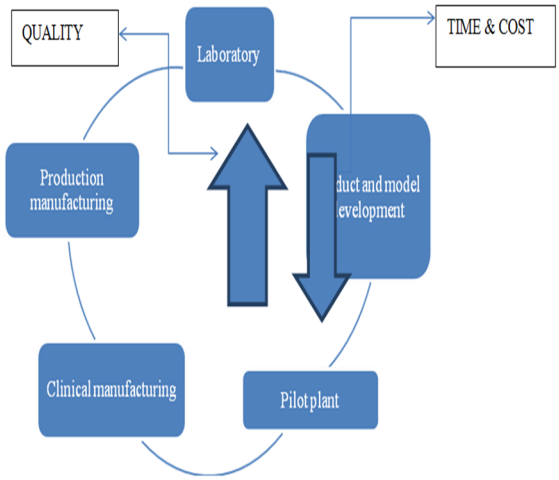

Figure 2: Business benefits from process analytical technology

Although benefits of PAT in the long-term are generally investment in process development does benefits the company and when it does not make any business sense. For example, a process step is not under any time constraints, does not represent a potential bottle neck, does not consume costly reagents and resources, and does not pose a risk of contamination or introduction of impurities, and then there may be little justification for investing in the monitoring, control, and optimization of that particular process step. The sensors available as analysis tools are not compatible with the process. Analyzer dependability, having small expertise in high specialized technology, in adequate validation of analyzer/software add with all these makes PAT associated risks too high and creates hesitance over change and remains as big hurdles for PAT implementation. But business models are changing and the importance of manufacturing's role in the financial performance of pharmaceutical companies are important. While the cost of restructuring production lines may be daunting to smaller companies, the savings gained from more efficient use of resources, reduced waste, faster product approvals and a lower risk of product recalls would outweigh the cost to implement PAT.

Regulatory view[4]

Much of the start for PAT comes from the initiative the US Food and Drug Administration (FDA) took in September 2004. Also the European Medicines Evaluation Agency (EMEA) started around that time an EU (European Union) PAT team, working in close cooperation with its US counterpart on the PAT topic. The FDA wants the industry to place its focus on the science of manufacturing and recognizes that significant regulatory barriers have inhibited pharmaceutical manufacturers from adopting state-of-the-art manufacturing practices within the pharmaceutical industry in the past. The FDA's PAT framework and its new risk-based approach for Current Good Manufacturing Practices (cGMPs) for the 21st century seek to address the problem by modernizing the regulations of pharmaceutical manufacturing, to enhance product quality and allow manufacturers to implement continuous improvement, leading to lower production costs.

The FDA talks about a 'desired state' of manufacturing with:

- Product quality and performance are ensured through the design of effective and efficient manufacturing processes.
- Product specifications based on mechanistic understanding of how formulation and process factors impact product performance.
- An ability to affect continuous improvement and continuous "real time" assurance of quality.

This new regulatory approach presents companies with the possibility of more attractive regulatory framework. The initiative's premise is that, if manufacturers demonstrate that they understand their processes, they will reduce the risk of producing poor quality products. They can then implement improvements within the boundaries of their knowledge without the need for regulatory review and will become a low priority for inspections.

Importance of PAT

PAT is now being set up in organization, it will help companies for the improvement of conformity along with the manufacturing regulations. PAT also helps to increase efficiency of the process and product design in terms of quality. It is a working principle or a frame work for operation.

Objectives of PAT[1,3]

- To design and develop process, which consistently ensure the quality of end product
- To identify, explain and manage the sources of variability affecting a process
- To prevent re-processing, rejects and scraps

- To improve energy and material use to increase its capacity
- To utilize dedicated manufacturing facilities
- To facilitate continuous process efficiency and to manage variability
- To improve safety to operator and to reduce human errors
- To reduce production cycle time by using online, in line or at line measurements and control

PAT tools

1. Multivariate tools[1]

Both the product and the production processes are complex multifactorial systems.

Insight in the production process and the interaction with the product requires complete multidimensional experiment data: modifying one factor at a time around the normal operation conditions is not sufficient.

The Design of Experiments (DoE) Theory is used to gather complete data sets allowing unveiling the underlying models.

Consecutively modeling software like Umetrics, Matlab, Camo etc., allows to derive a mathematical of the experiment data which simulates the system behavior.

These models can be MVDA (Multivariate data analysis) or other (e.g. Bayesian Networks). Once models are made, the same tools need to be used to evaluate the model and validate it with separate data sets.

2. Process analyzers[1,5]

Typical analyzers that will deliver input to allow online monitoring are such as Near Infrared Spectroscopy (NIR), Raman spectroscopy, Process GC (gas chromatography) analyzers. The process parameters, such as temperature, pH, pressure, flow which can easily be measured online, will be used as well. In addition, to that use characteristics of raw materials which were measured offline. A combination of scientific insight and experimental/modeling allows decisions to be made on the relevance and reliability of the mathematical relationships. Analyzation can be done for at -line, on-line and in-line.

a. At-line : Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream

b. On-line : Measurement where the sample is diverted from the manufacturing process and may be returned to the process stream

c. In-line : Measurement where the sample is not removed from the process stream and can be invasive or non-invasive

3. Process control tools[1]

Process insight delivers relevant process/product attributes. Online monitoring of these attributes should allow early detection of abnormal behavior. These attributes can be used to feed a classic or Advanced Process Control loop.

4. Continuous improvement and knowledge management tools[1]

Gaining process insight can allow the improvement of the process as well as improvement of the control strategies. Data and metadata (conclusions, observations etc.) gathered during the use of PAT should be archived to allow later reuse during a future improvement cycle.

Four key elements in PAT implementation:-

a. Building a science – based knowledge base complete process understanding at the mechanistic and first principle level.

b. Process monitoring and control determination of critical process parameters and critical quality attributes and selection of measurement, analysis and control mechanisms to adjust the process to provide the predicted quality of the product.

c. Validation of PAT system.

d. Regulatory strategies.

a. Building a science – based knowledge base

The PAT guidance emphasizes the need to develop a deep understanding of the underlying scientific principles behind pharmaceuticals manufacturing processes to determine the critical parameters to process and product quality. The knowledge base provided by the PAT approach is valuable in three main ways:

- It is a foundation for robust process and product design
- It facilitates continuous learning throughout the product life cycle
- It supports and justifies flexible regulatory paths for innovative new approaches

The design of experiments, and the capture and evaluation of analytical measurement data are essential parts of building the knowledge base.

Examples of sources of variation

- Variation in the raw material supplier manufacturing processes that impact the chemical and physical attributes of the supplied materials.
- Time based variation in manufacturing performance (e.g., between equipment maintenance events).
- Effects linked to planned changes to equipment/analyzer hardware and software of the system.

- Individual ways of working (i.e., variation attributable to people in manufacturing area).
- Change in the local environment (e.g. temperature, humidity and other environmental condition).
- Long term equipment ageing and degradation effects

b. Process monitoring and control

The understanding of the interaction between process and product is the basis for the design of the process monitoring, process control and QA strategies used in manufacturing PAT is an integrated approach in which the results obtained from the real time analysis of critical process control points are used to control the process in some way. During manufacturing, process parameters are adjusted (within clearly defined limits) to produce the desired product quality attributes at the process end point. The automation system required for this level of process control are available today and are used extensively in the chemical and petrochemical industries. Technologies used in PAT includes Near infra-red (NIR), Raman spectroscopy, UV – visible, Spectrophotometry, Fourier Transform Infrared (FTIR), X- Ray Powder Diffraction (XRPD), Terahertz Pulse (TP) spectroscopy, NIR microscopy, Acoustic Resonance (AR) spectrometry, thermal effusively, etc. NIR spectroscopy is the most popular and widely used technique.

c. Validation of PAT system[6]

The validation plan for a PAT system will typically include the validation of Software packages for data analysis. Process analyzer hardware and software process control software IT systems for the management, storage and backup of results.

ISPE has published a series of good practice guides for the industry on several topics involved in drug manufacturing. The most well-known is "The Good Automated Manufacturing Practice (GAMP) Guide for Validation of Automated Systems in Pharmaceutical Manufacture". The last major revision (GAMP 5) was released in February 2008.

The guidance generally states that pharmaceutical computer systems should be built with several key ideas in mind

1. Make product and process understanding clear.

2. Approach the life cycle from the standpoint of a quality management system.

3. Make life cycle activities scalable.

4. Ensure quality risk management is science-based.

5. Leverage supplier involvement into the system.

d. Regulatory strategies

FDA presentations indicate their anticipation that PAT implementation will eventually change the regulatory process. Documentation of quality by design during the pre-IND meeting, the end of phase-II meeting, and in regulatory submissions will allow early review and analysis of the CMC (chemistry manufacturing and control) section of an NDA by the FDA.

Addressing issues of concern and further quality by design can result in classification of the drug substances and drug process manufacturing as low risk.

A PAT policy development team of four subject matter experts has been established to work with industry to facilitate discussion on proposed pat approaches at an early stage and support FDA's sciences and risk based approaches to PAT.

Main Pharmaceutical Benefits from PAT[7]

In pharmaceutical R&D

- A deeper scientific and engineering understanding of manufacturing processes.
- Reduced product development times, more robust licensing packages, faster scale up, and faster time-to market for new products.
- Implementation of innovative manufacturing and quality strategies.

In pharmaceutical manufacturing:

- Reduced waste, right-first-time manufacturing, higher production asset utilization.
- Real-time quality assurance and validation.
- Movement toward real-time release of products.
- Lean manufacturing practices for reduced raw material, work-in-progress, and finished goods inventories.
- More robust product supply to the public.

Other benefits

- It decreases the processing cost, inventories
- It improves quality ,enhances supply reliability and reduces production change over time
- It meets all kinds of regulatory requirements

Risk assessment with PAT

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with final laboratory testing conducted on representative samples to ensure quality of the product.

This conventional approach has been successful in providing quality pharmaceuticals to the public[8].

The problem with this type of approach is that if at final testing final product fails to pass the quality specifications the whole batch has to be discarded incurring a huge loss to the organization including variability.

The relationship of variability with product is given in figure 4.

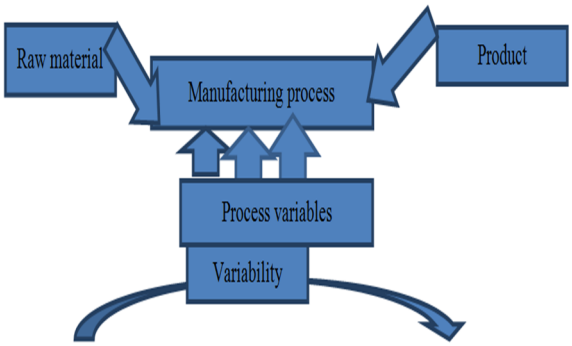

Figure 4: Relationship of variability with product

It would be acceptable to consider that raw materials used to manufacture pharmaceutical products can vary in their attributes such as moisture content, crystal structure etc. It would also be acceptable to consider that manufacturing equipment does not always operate in exactly the same fashion due to the inherent tolerance of the equipment and its components. Not only this, another problem is that if that particular representative sample is not up to the quality specification but the overall batch is good, in that case also the whole batch will be discarded based on the result of sample. It may also happen that the representative samples passes the test but the overall batch is of low quality and based on the result of the test sample. Product is released, only to be recalled later from the market. However, to overcome this type of uncertainty today significant opportunities exist which improves the efficiency of pharmaceutical manufacturing and quality assurance through the innovative application of novel product and process development, process controls and modern process analytical Chemistry tools. Pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond the challenges of new discoveries and ways of doing business. Pharmaceutical manufacturing continues to evolve with increased emphasis on science and engineering principles. Effective use of the most current pharmaceutical science and engineering principles and knowledge-throughout the life cycle of a product can improve the efficiencies of both manufacturing and regulatory processes[8]. So the PAT approach is in the vogue which is based on science and engineering principles for assessing and mitigating risks related to poor product and process quality[9]. The applications of PAT in pharmaceutical industry is given in table.1.

Table 1: Examples of PAT applications in the pharmaceutical industry[3]

Application	Process analyzer Statistical tool Observation	Process analyzer Statistical tool Observation	Process analyzer Statistical tool Observation
Rapid, accurate and continuous tablet identification	Acoustic resonance spectroscopy	Principle components Analysis (PCA)	A fast and non-destructive method for on-line analysis and label comparison before shipping, to avoid mislabelling of drug
Evaluation of content uniformity for low-dose tablets	NIR	PCA	NIR/PCA was used to predict content uniformity of low-dose tablets manufactured by a direct compression process
Determination of content of uncoated pharmaceutical Pellets	Near infrared	Partial least squares (PLS) analysis	NIR method was developed and validated for determination of active content ranging from 80-120% of the usual active content of the uncoated pharmaceutical pellets
Roller compaction process of dry Granulation	Thermal effusivity measurement using the effusivity sensor	--	Effusivity measurements were used to monitor the roller compaction process
Mechanical property determination of the tablet containing drug	Air-coupled excitation and laser interferometric detection	Iterative computational technique	Examination of the vibrational resonance frequencies can be directly correlated with the mechanical properties of the tablet providing a non- destructive technique for physical characterization of the tablet
Powder flow characterization	NIR	PLS	Real time information on the flowing cohesive powder. Mixture was used to avoid powder segregation or agglomeration and thus to maintain product quality.
Analysis of sustained-release tablet film coatings using terahertz pulsed imaging (TPI)	Terahertz pulsed spectroscopy (TPS)	--	Tablet coating thickness, coating reproducibility, distribution, and uniformity can be easily determined. The method was validated against optical microscopy imaging
NIR measurement of the potency of an API	NIR	PLS	Potency of heparin active pharmaceutical ingredient was determined by this non-destructive method

Active drug identification and content determination	NIR	PLS	NIR method was used for qualitative and quantitative determination of ranitidine in granules for compression, cores, and final tablet
Monitoring capsule manufacturing at small-scale level	NIR	PLS	PAT was utilized for testing of identity and quality of raw materials, for blend uniformity analysis, and for final content analysis of busulfan pediatric Capsules
Analysis of liquid formulations containing sodium chloride	Laser-induced breakdown spectroscopy (LIBS)	PLS	Method does not need any sample preparation and it is less time-consuming
Quantification of the active ingredient in pharmaceutical injectable formulations	NIR and UV–visible spectroscopy	PLS	More economical and less time-consuming and more beneficial method for quantification of the lysine clonixinate
Prediction of dissolution for a sustained-release dosage form	NIR	PLS	This method was used to identify differences in the composition of the coating polymers used for a tablet and thus assist with prediction of dissolution behaviour and process

CONCLUSION

PAT builds in process optimization and condenses risk of market criticism. It also develops the proficiency of process which leads to good consistency of the products. Understanding the process helps to gain knowledge which controls the better quality of product needed for the patients. Effective implementation of PAT done basis chemical, physical and mechanical properties of product more over on the assessment of risk. So PAT is a critical technology which shapes quality inside the product instead of making product quality.

REFERENCES

1) Bhupendra Shrestha, Hema Basnett, P Mohan Raj, Sita Sharan Patel, Mrinmay Das and Neelesh Kumar Verma Process Analytical Technology: A Quality Assurance Tool, Research Journal of Pharmacy and Yechnology. 2(2), 2009.

2) Randall.C. Willis, Process analytical technology regulations and review, American chemical society, February, 2004, 21-22.

3) Ravindra Kamble, Varghese, KR Sumeet Sharma, Venus Mahadik, Process Analytical Technology (PAT) in Pharmaceutical Development and its Application, International Journal of pharmaceutical Science review and research , November-December 2013, 212-223.

4) SIPAT the software heart of PAT: White paper, Siemens, 1-29.

5) Rakshith V. Thumar, Vidhi N. Kalola, Nishendu P. Nadpara, Parula B. Patel**,** A complete view of process analytical technology (PAT), IJPSRR, 17(1), 2012, 57-65.

6) Good Automated Manufacturing Practice (GAMP) Guide 4.0, International Society for Pharmaceutical Engineering (ISPE), July 2013.

7) White paper, Process Analytical Technology initiative expected to Invigorate Pharmaceutical Industry with Improved Quality, better efficiency and Improved profits, November 2014.

8) FDA, Guidance for industry: PAT - A framework for innovative pharmaceutical development, manufacturing and quality assurance; September 2004, 1-19.

9) Peter Scott, Process analytical technology in the pharmaceutical industry: a toolkit for continuous improvement; PDA Journal of Pharmaceutical Science and Technology. 60(1), 2006, 17-53.

Source of Support: Nil, **Conflict of Interest:** None.