Review Article

PROCESS ANALYTICAL TECHNOLOGY (PAT): THE PUSH FOR MODERN PHARMACEUTICAL MANUFACTURING

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ABSTRACT

The scientific, risk based framework outlined in this article Process Analytical Technology (PAT) is intended to support innovation and efficiency in pharmaceutical development, manufacturing and quality assurance. It is important to note that the term *analytical* in PAT is viewed broadly to include chemical, physical, microbiological, mathematical, and risk analysis conducted in an integrated manner. The PAT initiative was initially intended for traditional pharmaceutical manufacturers, but the FDA.s PAT guidance now clearly states that it applies to all manufacturers of human and veterinary drug products, as well as biologics regulated by the FDA's Center for Drug Evaluation and Research (CDER) and the Center for Veterinary Medicine (CVM). PAT is now mainly used in focusing on manufacturing process development, formulation development, design of experiments, data acquisition and chemo-metric approach, control of critical steps and intermediates, etc. In today's lean manufacturing environment, it's critical for companies of all sizes to focus on optimizing their production processes. By adopting the PAT framework and building-in quality on the front end, pharmaceutical manufacturers can more effectively maximize their production assets and will be better positioned to adapt quickly to market changes. Moreover, since the initiatives have the support of regulatory agencies, a successful PAT initiative can lead to regulatory incentives.

Keywords: Process analytical technology, Pharmaceutical industry, Quality management.

1. INTRODUCTION

There is very narrow definition for process analytical technology, which is as- Analytical technology used during process control. USFDA recommends to implement it into an initiative focusing on improving several aspects of pharmaceutical industries[1,2].

Food and Drug Administration (FDA) has suggested a definition for PAT which is, "PAT is considered to be a system for designing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes for raw and in-process materials and processes with the goal of ensuring final product quality."[3]

The underlying premise of PAT is- *quality should be built into product and testing, alone cannot be relied on to ensure product quality*. Quality should be built from selection of raw material to final product testing. PAT will boost collaboration between research and development (R&D), manufacturing departments, quality assurance (QA), quality control (QC), and information technology (IT) departments inside company and increased overall efficiency.

Process analytical technology (PAT) is a new innovative technology in which new analytical techniques are adopted by the pharmaceutical industries to design and improve the understanding and control of manufacturing processes.

Process Analytical Technology (PAT) is intended to support innovation and efficiency in pharmaceutical development, manufacturing, and quality assurance. The regulatory implementation strategy includes creation of a PAT Team approach to chemistry manufacturing and control (CMC) review and current good manufacturing practice (CGMP) inspections as well as joint training and certification of PAT review and inspection staff. Together with the recommendations in this guidance, our new strategy is intended to alleviate concern among manufacturers that innovation in manufacturing and quality assurance will result in regulatory impasse[4].

PAT is one element of broader process which has received some dynamic with FDA's GMP initiative for the 21st century and continues within the ICH process:

Q8: Pharmaceutical Development: "The aim of the pharmaceutical development is to design a quality product and the manufacturing process to deliver the product in a reproducible manner. It is basis for process mitigation."

Q9: Risk Management: "The focus should be to identify hazards that the potential for patient impact i.e. hazards that have the potential to affect product quality, safety and efficacy."[4]

1.1 As a TQMS tool

Process analytical technology is a part of Total Quality Management System (TQMS).Total Quality Management System is an aspect of management function that determines and implements the quality policy i.e. overall intensions and directions of an organization regarding

quality as formally expressed and authorized by the top management.

Objectives of TQMS[5]:-

- Provide high quality drug product to patients and prescribers.
- Prevent or reduce the recalls, salvaged products, defects, discrepancies, etc.
- To handle many types of changes to facilitate equipment and processes.
- To help in getting quality by design (QbD).

Concepts of TQMS[5]:-

- Quality
- Quality by design and product development
- Risk management
- Corrective action and preventive action(CAPA)

2. HISTORY

Conventional pharmaceutical manufacturing is generally accomplished using batch processing with laboratory testing conducted on collected samples to evaluate quality. This conventional approach has been successful in providing quality pharmaceuticals to the public. However, today significant opportunities exist for improving pharmaceutical development, manufacturing, and quality assurance through innovation in product and process development, process analysis, and process control.

Unfortunately, the pharmaceutical industry generally has been hesitant to introduce innovative systems into the manufacturing sector for a number of reasons. One reason often cited is regulatory uncertainty, which may result from the perception that our existing regulatory system is rigid and unfavorable to the introduction of innovative systems. For example, many manufacturing procedures are treated as being frozen and many process changes are managed through regulatory submissions. In addition, other scientific and technical issues have been raised as possible reasons for this hesitancy. Nonetheless, industry's hesitancy to broadly embrace innovation in pharmaceutical manufacturing is undesirable from a public health perspective. The health of our citizens (and animals in their care) depends on the availability of safe, effective, and affordable medicines[1-3].

Pharmaceuticals continue to have an increasingly prominent role in health care. Therefore pharmaceutical manufacturing will need to employ innovation, cutting edge scientific and engineering knowledge, along with the best principles of quality management to respond to the challenges of new discoveries (e.g., novel drugs and nanotechnology) and ways of doing business (e.g., individualized therapy, genetically tailored treatment). Regulatory policies must also rise to the challenge.

In August 2002, recognizing the need to eliminate the hesitancy to innovate, the Food and Drug Administration (FDA) launched a new initiative entitled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach."

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 the manufacturing and regulatory processes.

PAT was used from decades in other manufacturing industries like fine chemicals, petroleum's, bioprocess industries, etc. The process analytical technology term is generated from the process analytical chemistry (PAC). PAC was began some 70 years ago. The modern period of PAC is essentially began with the formation of center of process analytical chemistry (CPAC) in 1984.[4]

Process Analytical Chemistry is the art and science of making measurements for the purpose of control of large scale chemical processes. PAC is largely for problem solving purpose as well as a way to determine the composition of the desired products in process.[2-3]

3. PAT FRAMEWORK

The framework is founded on process understanding to facilitate innovation and risk-based regulatory decisions by industry and the Agency. The framework has two components:

3.1 Components

1. A set of scientific principles and tools supporting innovations.
2. A strategy for regulatory implementation that will accommodate innovation.

3.2 Goals

1. To design and develop well understood processes that will consistently ensure a predefined quality at the end of manufacturing processes.
2. Manufacturers are encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology
3. Management of the Agency's Risk-Based Approach encourages innovation in the pharmaceutical manufacturing sector
4. Agency resources are used effectively and efficiently to address the most significant health risks
5. The most up-to-date concepts of risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining product quality

3.3 Process Understanding

1. Sources of variation in process:

All critical sources of variability are identified and explained, product quality attributes can be accurately and reliably predicted over the design space established for materials used, process parameters, manufacturing, environmental, and other conditions.

2. Process understanding is inversely proportional to the risk.

3. It is a key in the future of manufacturing:

A focus on process understanding can reduce the burden for validating systems by providing more options for justifying and qualifying systems intended to monitor and control biological, physical, and/or chemical attributes of materials and processes

The simple meaning of process understanding is expressed by,

Process understanding=design + predictability + capability

3.4 PAT tools

1. Multivariate tools for design, data acquisition and analysis:

From a physical, chemical, or biological perspective, pharmaceutical products and processes are complex multi-factorial systems. There are many development strategies that can be used to identify optimal formulations and processes. The knowledge acquired in these development programs is the foundation for product and process design

A. Multivariate data acquisition tool (MDAT):

This is a new advanced software package used for data acquisition.

B. Multivariate Analysis (MVA):-

It is based on the statistical principles of multivariate statics, which involves observations and analysis of more than one statistical variable at a time.

2. Process analyzers:

Process analyzers typically generate large volumes of data. Some process analyzers provide nondestructive measurements that contain information related to biological, physical, and chemical attributes of the materials being processed. These measurements can be:

- At-line: Measurement where the sample is removed, isolated from, and analyzed in close proximity to the process stream.
- On-line: Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.
- In-line: Measurement where the sample is not removed from the process stream and can be invasive or noninvasive

Advances in process analyzers make real time control and quality assurance during manufacturing feasible. However, multivariate methodologies are often necessary to extract critical process knowledge for real time control and quality assurance.[4]

3. Process control tool:

It is strong link between product design and process development.

Design and optimization of drug formulation and manufacturing process within PAT framework includes following steps;

A. Identify and measure critical material and process attributes relating to product quality.

B. Design process control.

4. Continuous improvement and knowledge management tools:

It is a paper system or software packages which accumulates QC data acquired over the time for specific processes with aim of defining process implementing and monitoring process improvement.[4]

4. PAT IMPLICATIONS[4]

4.1 Implications on organization:-

4.1.1 Implication on personnel:-

- ✓ Qualification or skills
- ✓ Training (six sigma training)

4.1.2 Implications on management:-

- ✓ Organization
- ✓ Outsourcing
- ✓ Communication
- ✓ Regulatory

4.2 Implications on QA approach:-

- ✓ Audits
- ✓ Documentation
- ✓ Validation

4.3 Implications on the process:-

4.3.1 Implications on process understanding

4.3.2 Implications on production related QA\QC

- ✓ QC testing
- ✓ Continuous improvement

4.3.3 Implications on process technology

- ✓ Continuous production.

- ✓ New software's or tools and new methods

5. EXAMPLES OF ANALYTICAL METHODS USED IN PAT

Mid 80's: Near Infra Red (NIR) Spectroscopy used to control fermentation.

Early 90's: NIR used to qualify excipients and active pharmaceutical ingredients.

Late 90's: New technologies such as Raman spectroscopy, FTIR, NIR, HPLC, GC, MS, NMR, Ultrasound, etc are used.

Currently: Real time monitoring of vial filling, near infrared chemical imaging (NIR-CI), robotics, MIR process quantum cascade lasers in situ analyzers.[4]

Figure 1: Robotics used in PAT

5.1 NIR technology

- Used to qualify excipients and API.
- NIR spectra informative about product structure and overall quality.
- Used for identification and quality testing of raw materials.

5.1.1 Near-infrared Chemical Imaging (NIR-CI)

NIR-CI adds a completely new dimension (pun intended) to conventional NIR spectroscopy. It offers the ability to obtain high fidelity, spatially resolved pictures of the chemistry of the sample. Elucidation of compositional heterogeneity and structure is invaluable for both the development and manufacture of solid dosage forms. NIR image can be used to determine content uniformity, particle sizes, and distributions of all the sample components, polymorph distributions, moisture content and location, contaminants, coating and layer thickness, and a host of other structural details. Through the development phases of preformulation and scale-up, NIR-CI can be used to identify precisely the elusive critical control parameters that will affect the performance of the finished product. The technique is fast and nondestructive and can be used independently or in concert with other techniques, such as dissolution analysis, to rapidly diagnose potential production problems. NIR-CI instrumentation also is rugged and flexible, suitable for both the laboratory and the manufacturing environment. Therefore, analysis methods developed in the laboratory often can be tailored for implementation near-line or at-line. NIR-CI also is massively parallel NIR spectroscopy, making the technique well-suited for high through put at-line and even on-line applications.[7]

5.2 Raman spectroscopy

- Accurate determination of active pharmaceutical ingredients.
- Qualitative analysis of pharmaceutical products inside packaging.[4]

6. REAL TIME RELEASE (RTR)

RTR is a system of release that gives assurance that the product is of intended quality, based on the information collected during the manufacturing process, through product knowledge and on enhanced process understanding and control.

RTR testing provides greater assurance of product quality than end product testing (EPT).[8]

7. BENEFITS FOR INDUSTRIES[4,8-10]

- ✓ Reducing production cycle times.
- ✓ Better process understanding and control.
- ✓ Reduces or prevents rejects, scraps and reprocessing.
- ✓ Better management.
- ✓ Reduce inspection frequency.
- ✓ Better and more stable products.
- ✓ Increase automation.
- ✓ Faster batch release.
- ✓ Improving energy and material use and increasing capacity.

8. CONCLUSION

This article provides a valuable information regarding innovations in pharmaceutical industries. The FDA supported PAT initiative appears to have gathered significant pace and momentum during the past years or so, and undoubtedly will have major impact upon the way pharmaceutical manufacturing is conducted in the future. The basic message is not just the implementation of more in process measurements to shorten existing quality assurance–quality control times but to embrace the concept of process understanding, ultimately leading to process optimization. In order to accomplish this, the industry will need to look toward new technologies that can provide true insight into the component relationships and physical forces that drive and determine the quality and performance of pharmaceutical products.

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