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PROCESS ANALYTICAL TECHNOLOGY (PAT) - AS A CULTURE OF INNOVATION

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ABSTRACT: The pharmaceutical industry is in rapid transition from a supply-driven market to a demand and service-driven market where manufacturing efficiency and responsiveness will play a critical role in future success. To overcome this there is growing enthusiasm in the industry for the many potential gains offered by Process Analytical Technology, a new FDA initiative that aims to foster improvements in manufacturing efficiency and quality analysis. Pharma Industry is facing growing demands for increased productivity and reduced manufacturing costs and also has to meet the evolving need for higher quality standards and higher drug expectations The regulatory area appears to be rapidly evolving, with PAT initiative to be the first major change in the GMP's in over 25 years that is based on increased scientific understanding and less on an empirical based approach. PAT is important because, if it is successfully introduced, it will pioneer a new concept of regulation of quality in the 21st century.The PAT Approach is based on steps, strategy, cost, benefits and rules during implementation of pat.
Key words:-Process analytical technology (PAT), FDA, PAT approach, Tools, Strategy of implementation.

INTRODUCTION

PAT is System for continuous analysis and control of manufacturing processes based on real time measurements or rapid measurement during processing, of quality and performance attributes of raw and in process materials and process which assures acceptable end product quality at the completion of the process.[1]

Thus PAT is a system for:

- Designing, analyzing, and controlling manufacturing.
- Timely measurements.
- Critical quality and performance attributes.
- Raw and in-process materials.
- And processes.

The goal of PAT is to understand and control the manufacturing process, which is consistent with our current drug quality system; quality cannot be tested into products; it should be built-in or should be by design

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." This initiative has several important goals, which ultimately will help improve the public's access to quality health care services. The goals are intended to ensure that:

- The most up-to-date concepts of risk management and quality systems approaches are incorporated into the manufacture of pharmaceuticals while maintaining product quality
- Manufacturers are encouraged to use the latest scientific advances in pharmaceutical manufacturing and technology
- The Agency's submission review and inspection programs operate in a coordinated and synergistic manner
- Regulations and manufacturing standards are applied consistently by the Agency and the manufacturer
- Management of the Agency's Risk-Based Approach encourages innovation in the pharmaceutical manufacturing sector
- Agency resources are used effectively and efficiently to address the most significant health risks

To support Process Analytical Technology activities, FDA created:

- A PAT committee composed of senior pharmaceutical and generic manufacturers; government officials; and private and academic consultants to the pharmaceutical industry. This subcommittee reported to FDA's Advisory Committee for Pharmaceutical Science and provided recommendations on issues to be addressed in the proposed FDA guidance for adoption of PAT by regulated industry.
- A Steering Committee comprised of senior managers in FDA, which oversees PAT activities for the Agency.
- A PAT Team to approach to CMC review and CGMP inspection. This team of reviewers, compliance officers and investigators is being jointly trained and certified on PAT issues and new technology to manage the review and inspection process.
- A PAT Research Team in the Office of Testing and Research, which conducts research to provide a scientifically based policy development process and support for the PAT Team.
- An Office of Pharmaceutical Science PAT Policy Development Team which will support and advise the PAT Team.[2]

PAT INITIATIVE

PAT is important because, if it is successfully introduced, it will pioneer a new concept of regulation of quality in the 21st century. Thus the various reasons for the pat initiative are as follows:

- Nowadays there is an increasing trend towards manufacturing related problems.
- Low manufacturing process efficiency—cost implications.
- The burden on FDA resources has increased tremendously with the up coming pharmaceuticals companies.
- Some larger global pharmaceutical companies are being very keen for Innovation, modernization and adoption of new technologies, but the other small companies are less keen towards adoption of new technology.

APPROACH TO THE PAT

The basis for the PAT awareness document was the evaluation of 11 PAT case studies. The following benefits depend on the degree of the PAT implementation:

1: Quality

• Better quality definition and analysis methods
• Reduction of complaints and recalls

2: Process[1]

Introduction and implementation of new process automation technologies including sensors, analytical devices, and process control technologies is not a mandatory prerequisite for PAT. PAT also can be achieved with existing process and control equipment. The benefits of implementing PAT in the process have been estimated to be very positive.

3: Risk

Risk assessment is a positive state-of-the-art methodology for risk detection and minimization, but currently in the companies sampled independent from PAT. Risk assessment will become a key integral method within PAT.

4: Costs

In all other cases, it is still too early for a meaningful calculation. Practical experience, as far as available, revealed fewer rejected batches, fewer deviations, increased yield with higher Overall Equipment Effectiveness (OEE), fewer consumables, less waste, and fewer reworks.

5: Personnel

The shift to PAT-based thinking encourages the communication between different departments. A better process understanding is obtained. There are hints to a slight increase in personnel safety.

6: Tools[3]

A clear result of the investigation is that more process data is recorded, analyzed, and stored. The data is additionally used within the batch documentation. In most cases, the data is used for advanced process control and the prediction of process deviations. Applied analytical methods: NIR, MIR, Raman, laser diffraction, mass spectroscopy, accelerated dissolution testing, etc. Applied statistical methods: MVDA, DMAIC, etc.

7: Time

• Faster decisions for on-line quality assessment and faster and earlier decisions on waste material
• Due to automated data acquisition, shorter transition time from raw data to meaningful process information
• Material variability is detected earlier

8: Validation

In total, a lower effort for validation is expected, but more effort has to be put into facility, equipment, and software validation during PAT implementation

PAT projects have an impact on the organization of pharmaceutical companies and increase the interdisciplinary communication between departments.

9: Regulatory

Regulatory issues have a strong impact on:

•The frequency of scientific-based contacts and communications with regulatory bodies
• Earlier and more frequent contact before and during the implementation phase
• The kind of documentation that will undergo changes (more precise and deeply science-based, earlier documentation during design is expected)
• change control (a positive impact is anticipated)

TOOLS FOR PAT[2]

There are many current and new tools available that enable scientific, risk managed pharmaceutical

development, manufacture, and quality assurance. These tools , when used within a system can provide effective means for acquiring information to facilitate process understanding, develop risk mitigation strategies, achieve continuous improvement and share information and knowledge in PAT framework, these tools can be categorized according to the following.

A. Multivariate Data Acquisition and Analysis

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

Methodological experiments (e.g., factorial design experiments) based on statistical principles of orthogonality, reference distribution, and randomization provide effective means for identifying and studying the effect and interaction of product and process variables. Traditional one-factor-at-a-time experiments do not effectively address interactions between product and process variables. Interactions essentially are the inability of the one factor to produce the same effect on the response at different levels of another factor.

B. Process Analyzers or Process Analytical Chemistry Tools

Chemical industry drivers of productivity, quality, and environmental impact have supported major advancements in this area. Available tools have evolved from those that take simple process measurements, such as pH, temperature, and pressure, to those that measure chemical composition and physical attributes. Some modern process analysis tools provide nondestructive measurements that contain information related to both physical and chemical attributes of the materials being processed. These measurements can be:

- **off-line** in a laboratory
- **at-line** in the production area, during production close to the manufacturing process
- **on-line** where measurement system is connected to the process via a diverted sample stream; the sample may be returned to the process stream after measurement
- **in-line** where process stream may be disturbed (e.g., probe insertion), and measurement is done in real time
- **noninvasive**, when the sensor is not in contact with the material (e.g., Raman spectroscopy through a window) in the processor, the process stream is not disturbed

Many of these recent innovations make real-time control and quality assurance during manufacturing feasible. However, multivariate mathematical approaches are often necessary to extract this information from complex signatures and to correlate these results to a primary method of analysis.

C. Process Monitoring, Control, and End Points

Design and optimization of drug formulations and manufacturing processes within the PAT framework can include the following steps (the sequence of steps can vary):

- Identify and measure critical material and process attributes relating to product quality
- Design a process measurement system to allow real time or near-real time (e.g., on-, in-, or at-line) monitoring of all critical attributes
- Design process controls that provide adjustments to ensure control of all critical attributes
- Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes

Therefore, it is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical quality attributes.

Process monitoring and control strategies are intended to monitor the state of a process and actively manipulate it to maintain a desired state.

D. Continuous Improvement and Knowledge Management

Continuous learning through data collection and analysis over the life cycle of a product is important. Data can contribute to justifying proposals for post approval changes including introduction of new technologies. Approaches and information technology systems that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the regulatory bodies.

STRATEGY FOR IMPLEMENTATION

The Agency understands that to enable successful implementation of PAT, flexibility, coordination, and communication with manufacturers is critical. The Agency believes that current regulations are sufficiently broad to accommodate these strategies. Regulations can effectively support innovation when clear, effective, and meaningful communication exists between the Agency and industry, for example, in the form of meetings or informal communications.

The first component of the PAT framework described above addresses many of the uncertainties with respect to innovation and outlines broad principles for addressing anticipated scientific and technical issues. This framework should assist a manufacturer in proposing and adopting innovative manufacturing and quality assurance. The Agency encourages such proposals and has developed a regulatory strategy to consider such proposals. The Agency's regulatory strategy includes the following:

- A PAT team approach for CMC review and CGMP inspections.
- Joint training and certification of PAT review, inspection and compliance staff.
- Scientific and technical support for the PAT review, inspection and compliance staff.
- The recommendations provided in this guidance.

Proposed Steps to a PAT Implementation[4]

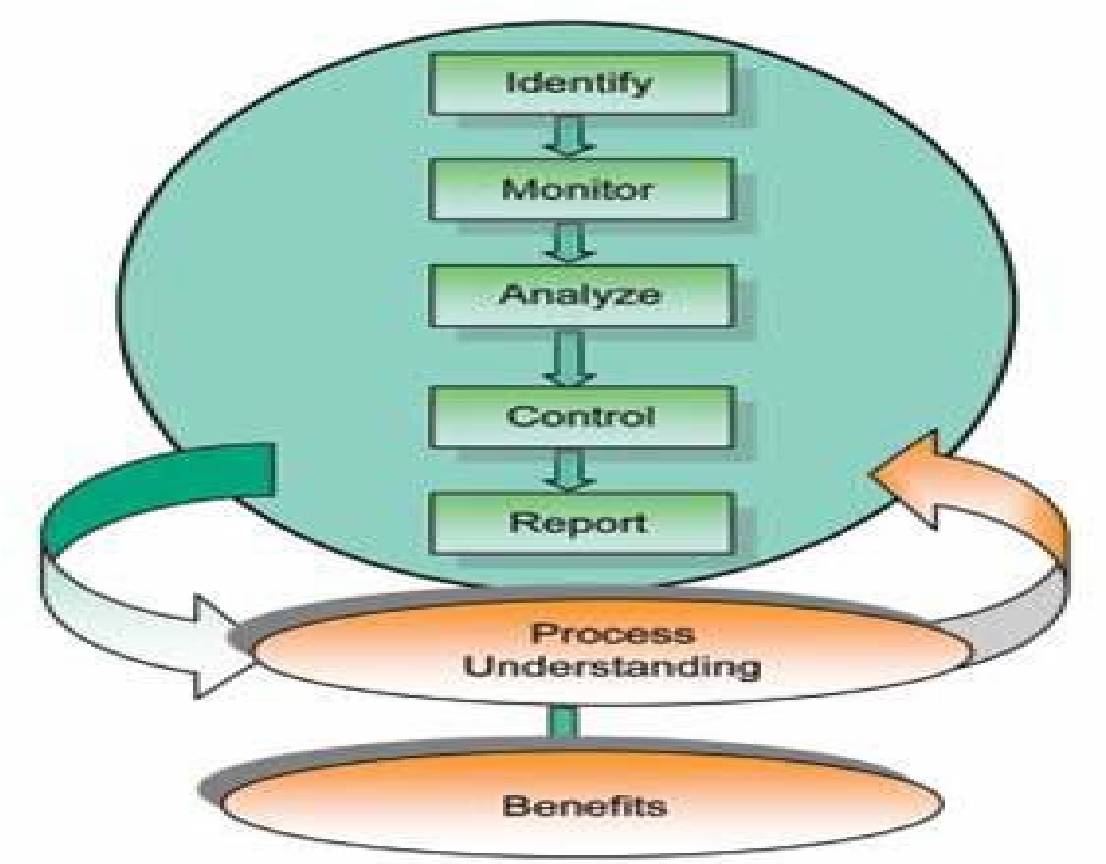

Fig 1: Proposed Steps to a PAT Implementation

From above Fig1 it can be concluded that for PAT implementation various terms were consider they can be explained as follows ..

1. **Identify**: this step includes the process of identifying an opportunity that would benefit from the PAT approach, as well as identifying the critical quality at tributes that need to be monitored and controlled in the process.
2**. Monitor**: the next step after identifying the critical quality attributes would be to monitor them. Monitoring is usually achieved using on-line instruments. Recent advances in on-line analytical instrumentation have encouraged more online monitoring of parameters of interest. The simple premise is that we cannot control something we cannot monitor. The monitoring step allows us to collect data for the CQA of interest and evaluate the effect of adjusting the CQA on the overall process efficacy.
3. **Analyze**: the analysis step ensures that once we have identified our critical quality points and monitored them, we employ statistical analysis to determine how the critical quality attribute is related to the overall process efficacy. This step includes the development, verification, and validation of any statistical models that could define the process. Experimental studies, engineering test plans, and retrospective data analysis are methods that we employ to analyze the CQA relationship to the overall process.
4. **Control:** after we have analyzed the relationship between the CQA and overall process efficacy and developed any statistical models, the next step in the PAT effort would be to control the process to ensure that the CQA is within specified limits at all times. This is the most critical step of the PAT roadmap that essentially ensures that "real-time" quality assurance is met.
5. **Report** The reporting element encompasses any tools that aid in assuring that the process was in fact in control through out the processing period. Reporting tools serve two purposes - they allow for data to be reported in a fashion that aids in developing process understanding, and they allow for any exceptions from the "ideal state" to be documented in the final release records.

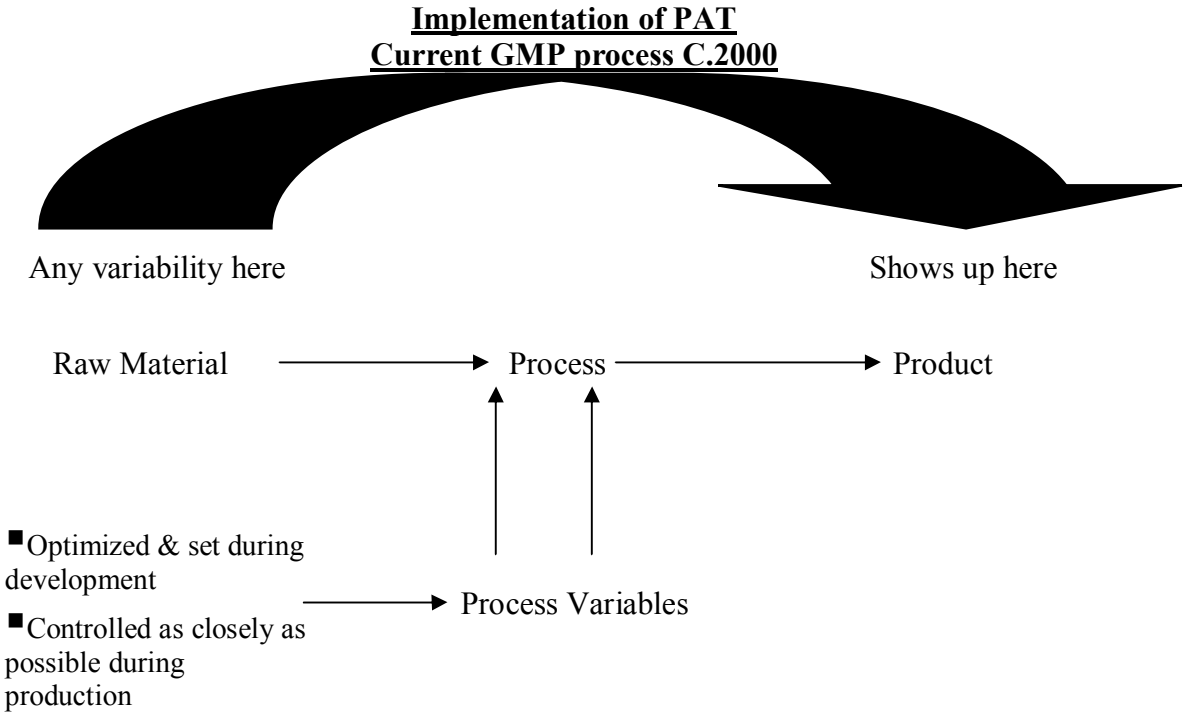

Fig 2: Current GMP process

In the current manufacturing process the variability present in the raw material is checked at the end of the process when the final product testing is done. The process variables which are incorporated in the process are optimized and set during development.[5]

According to above fig 2 it shows that process variables are controlled as closely as possible during production process only no changes can be made at other stages.

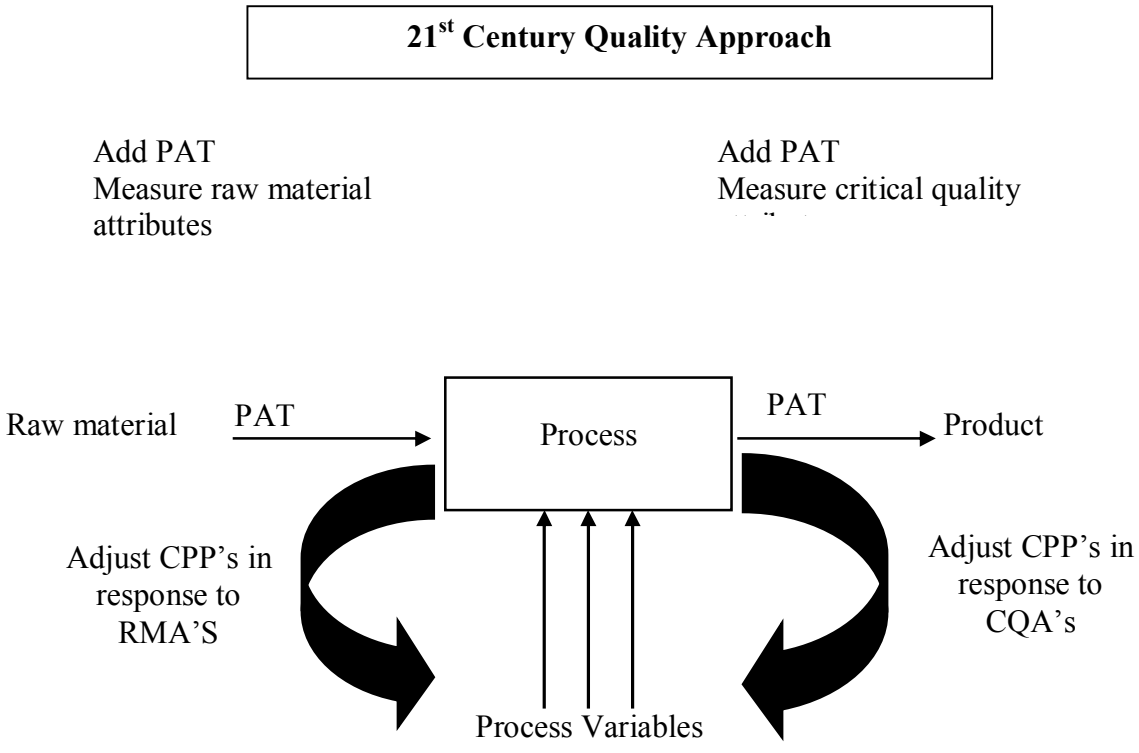

Fig 3: 21st Century Quality Approach

Combination of feed forward and feedback control of CPP's provides even greater control of critical quality attributes[6]

Quality is built into the pharmaceutical products during the process itself with help of PAT.
Steps involved for implementation of PAT:

Step 1:

Adjust the critical process parameters in response to raw material analysis.
The various critical parameters adjusted are

- **Chemical attributes**: identity, purity.
- **Mechanical attributes**: particle size, particle shape, inter and intra particulate bonding.

Step 2:

Adjust the critical process parameters in response to critical quality attributes like content uniformity, moisture content, dissolution rate, etc.
The feed forward and backward control is the degree of flexibility in process conditions (time) should be applied to manage differences in physical attributes of material being processed[7]
So Fig 3 helps us in knowing that an approach can be justified and established with differences in physical attributes and process end points are used to control the process.

COST OF IMPLEMENTATION OF PAT

The instrumentation needed for PAT is mainly probes, sensors, etc., which will lead to increase in the actual cost of equipment. The SOP'S too are needed to be changed or amended. Thus the process cost is also increased[8]

Most facilities have the processes in place

- Sensor and on-line technology can be adapted, if not installed.
- Data acquisition systems may be in-place.
- SCADA, BMS, and Computerized manufacturing systems may be in place.
- SOPs will have to be changed, as the sampling will not be needed each time. Also the data collection online will vary with PAT application.
- New products, processes and R&D technology transfer are ideal for PAT.
- IQ, OQ, PQ documentation is performed once.
- Validation is simpler as the product and process are completely understood.

BENEFITS OF PAT

- Cost reduction in manufacturing.
- Immediate action if quality is not met.
- Better and more stable products.
- Computerized data obtained will be of easier regulatory adherence.[9]

CONCLUSION

PAT promises to deliver a new culture to the pharmaceutical industry - a culture of innovation. Automation deployment needs to support this FDA encouraged effort by providing an infrastructure that fosters integrated data management and data analysis abilities across the entire process. This leads to improved process understanding, which in return allows for the implementation of additional automation and PAT functions where it is determined to be most beneficial for product safety and yield. The presented concept of scalable automation enables an efficient addition of these automation and PAT functions throughout the entire lifecycle of the facility.

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