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Review Article

Process analytical technology – A review of game changer regulatory framework by US FDA

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ABSTRACT

The concept of process analytical technology is introduced with the purpose of providing important information after the analysis of critical quality parameters which can have direct or indirect impact on the product quality. This type of information is helpful in maintaining the product quality while keeping the manufacturing cost low. The implementation of PAT will potentially improve the operational control and compliance as per regulatory guidelines for continuous real time quality assurance during manufacturing. The concept is relatively new for both academia and industry hence Considerable amount of study has been carried out to explore the various aspects of PAT guidelines and their successful implementation. This review mainly contains introduction and background of PAT guidelines as the first step in QBD implementation. Detailed understanding of analysis and selection of suitable analytical technique is the most important aspect of PAT guidelines. These analytical techniques will even play crucial role at the time of scale up and detailed evaluation of drug and dosage forms. The main purpose of this review is to understand the right perspective of PAT guidelines towards the goal of achieving products with highest quality.

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1. Introduction

In the absence of modern guidelines for achieving quality the conventional pharmaceutical manufacturing was accomplished by batch processing in controlled environment followed by lab testing of randomly selected samples to check the quality. This approach has been able to provide quality pharmaceutical products to the public till date. However with the emergence of new knowledge for improving quality of pharmaceutical products via bringing new changes and technologies in product development, manufacturing and quality assurance have affected the quality of pharmaceuticals dramatically.

However pharmaceutical companies always have apprehensions in accepting and implementing new

technologies and innovative systems in their routine activities due to various reasons. One such reason would be the regulatory uncertainty where it is very difficult to introduce new innovative systems owing to the rigid and unfavorable current regulatory systems. Other possible reason could be scientific and technical issue. However the health of public is most important aspect of any regulatory authority in any part of world and thus pharmaceutical companies have no choice but to accept new technologies and innovative systems in order to keep check on the quality of pharmaceutical products. All pharmaceutical companies need to adopt innovation, latest cutting edge technology and best principles pertaining to quality management to stay updated and relevant in the time of rapidly changing technologies in the field of pharmaceutical manufacturing.

Taking initiative to remove apprehensions of pharmaceutical companies and to ensure public health

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and safety, in August 2002, the US FDA launched new guidelines called “Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach” within view to achieve following goals

1. Incorporation of most up to date concepts of risk management and quality system approaches in pharma manufacturing
2. To encourage pharma manufacturers to use the latest scientific technology.
3. To achieve synergy between US FDA’s submission review and inspection programs.
4. To apply regulations and manufacturing standards continuously to pharma manufacturing.
5. To encourage innovations in pharma manufacturing sector by risk based approach management.
6. To use all resources effectively and efficiently to achieve quality products^{1,2}

2. PAT framework

As per The US FDA the PAT is a system for designing, analyzing and controlling manufacturing by checking in process critical quality and performance attributes to ensure the final quality of product. The PAT guidelines are result of integration of various quality related aspects of chemical, physical, microbiological, mathematical and risk analysis. As per the US FDA the quality is not the final attribute to be tested but it should be built in or should be by design. The goal of PAT is to improve the understanding of this concept of quality and to control the manufacturing process to achieve consistent quality products.

The comprehensive understanding of following points is needed to build quality products in pharma industry:

1. The intended therapeutic objectives; patient population; route of administration; and pharmacological, toxicological, and pharmacokinetic characteristics of a drug
2. The chemical, physical, and biopharmaceutical characteristics of a drug
3. Design of a product and selection of product components and packaging based on drug attributes listed above.
4. The design of manufacturing processes using principles of engineering, material science, and quality assurance to ensure acceptable and reproducible product quality and performance throughout a product’s shelf life.

The expectation from the PAT framework is to design and develop well understood processes. These processes will further be helpful to ensure consistent predefined quality at the end of the manufacturing process. More ever these processes could reduce risk to quality and regulatory concerns while improving the efficiency. Gains in quality,

safety and/or efficiency will vary depending on the process and the product, and are likely to come from:

1. Reducing production cycle times by using on-, in-, and/or at-line measurements and controls
2. Preventing rejects, scrap, and re-processing
3. Real time release
4. Increasing automation to improve operator safety and reduce human errors
5. Improving energy and material use and increasing capacity
6. Facilitating continuous processing to improve efficiency and manage variability³

3. Principles and Tools

The pharmaceutical manufacturing includes numerous unit operations. Regular modulation of certain properties of materials is observed during the manufacturing process. However these modulations must be made considering the quality attributes of the incoming materials and their process ability for each unit operation. In recent past considerable work has been done in developing analytical methods for chemical attributes i.e. estimation of purity and the identification of the chemicals. Effective processes pertaining to management of physical attributes of materials need a sound understanding of various attributes, critically affecting the product quality. Owing to the complex nature of these attributes pertaining to material it is always challenging to deal with. This is primarily due to the difficulties associated with the collection of representative samples.

3.1. PAT tools

There are many tools available which can be used properly to understand processes, improvement strategies, and the development of risk mitigation strategies. Tools used in PAT framework can be classified in following categories. These tools can be used individually or in a combination for various unit operations, manufacturing processes or quality assurance:

1. Multivariate tools for design, data acquisition and analysis
2. Process analyzers
3. Process control tools
4. Continuous improvement and knowledge management tools

3.1.1. Multivariate tools for design, data acquisition and analysis

Almost all pharmaceutical processes are complex multi factorial systems. The knowledge gained during the development of various strategies pertaining to the analysis or the manufacturing will serve as the foundation for

the product and process design. With the help of this knowledge and understanding companies can justify necessary innovations in manufacturing and post approval changes to various regulatory agencies. Use of various multivariate mathematical approaches such as statistical design of experiment, response surface methodology, process simulation and pattern reorganization tools in combination with knowledge management systems can be helpful in achieving benefit of developing effective and efficient processes.

In order to study the interactions of product and process variables it is necessary to use methodological experiments based on statistical principles of orthogonality, references distribution and randomization.

Information collected from structured experiments during product and process development support the development of knowledge systems for a particular product and its processes. Information from various sources and projects become overall knowledge base of the institution. In future this knowledge base can be exploited for the pattern determination and future development projects. Various process simulation models can also be developed based on this knowledge base to help understanding new process development in shorter period of time.

These tools play very crucial role for the identification and the evaluation of products and process variables which are critical to product quality and performance. Also they help in the identification of potential failure modes and mechanisms along with quantifying their effects on product quality.

3.1.2. Process analyzers

Major advancement in the field of process analysis has been observed due to the support of various industrial drivers of productivity, quality and environmental impact. Considerable evolution has been seen in available tools for the measurement of various process parameters. Some process analyzers provide nondestructive measurements that contain information chemical, physical and biological attributes of materials being processed. These measurements can be:

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

In a PAT system, batch records must be prepared with all scientific and procedural information of high process quality and product conformance. Batch records can have series

of charts depicting acceptance range, confidence intervals and distribution plots showing measurement results. Ease of secure access to these data is important for real time manufacturing control and quality assurance. Installed information technology systems should accommodate such functions. Measurements must be collected in the form of absolute number or value of the attribute under the testing. The useful information for a process control can be obtained by knowing measurement differences in material before and during the process.

3.1.3. Process control tools

The effective control of all critical quality attributes can be achieved by establishing a strong link between product design and process development. The reason for having effective process monitoring and control strategies is to monitor and actively manipulate the state of process to achieve or maintain desired state. Organizations must develop strategies to comply with attributes of input materials, accuracy and the robustness of process analyzers to measure critical attributes and to achieve desired process end point with precision in terms of finished products.

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

1. Identify and measure critical material and process attributes relating to product quality.
2. 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.
3. Design process controls that provide adjustments to ensure control of all critical attributes.
4. Develop mathematical relationships between product quality attributes and measurements of critical material and process attributes.

While operating under the PAT framework the concept of fixed time as end point is not relevant compare to the achievement of the desired material attributes. However a range of acceptable process window in terms of time is necessary to achieve at the time of manufacturing phase and must be evaluated and the significant deviation from the acceptable process times should be considered.

In a PAT framework the demonstration of validation is done by continuous quality assurance. In this the process is continually monitored, evaluated and adjusted using validated in process measurements, tests, controls and process end points. Risk-based approaches are suggested for validating PAT software systems. The recommendations provided by other FDA guidance, such as General Principles of Software Validation should be considered. Other useful information can be obtained from consensus standards, such as ASTM.

3.1.4. Continuous improvement and knowledge management

It is very important to learn and understand through data collection and analysis over the life cycle of a product. This data can be used to justify proposals for post approval changes. Organizations must find opportunities to improve the application aspect of available products and process knowledge during regulatory decision making. The benefits of knowledge base is maximum when there is a mechanism to understand the relevant multi factorial relationship as well as tools to evaluate the applicability of this knowledge in different scenarios. This can be achieved by utilizing the technological advancement in the field of information technology.

3.1.5. Risk-based approach

In any established quality system there is always an inverse relationship between the level of process understanding and the risk of producing a poor quality product. Less restrictive regulatory approaches can be used to manage changes where processes are well understood. Due to this a focus on process understanding can be useful in developing risk based regulatory decisions and innovation.

Note that risk analysis and management is broader than what is discussed within the PAT framework and may form a system of its own.

3.2. Integrated systems approach

In order to satisfy the need of patient and the industry, organizations need technologically advanced integrated systems for the evaluation and timely application of tools and systems critical to make good quality products. Principally the advancements that have occurred brings product development, manufacturing, quality assurance and information/knowledge management functions very close that these areas should be coordinated in an integrated manner. Therefore, upper management support for these initiatives is critical for successful implementation.

The Agency recognizes the importance of having an integrated systems approach to the regulation of PAT. Therefore, the Agency developed a new regulatory strategy that includes a PAT team approach to joint training, certification, CMC review, and CGMP inspections.

3.3. Real time release

In real time release agency checks the ability of an organization to evaluate and ensure the acceptable quality of in-process and/or final product based on process data. Normally the PAT component of real time release deals with a valid combination of assessed material attributes and process controls. Direct and/or indirect process analytical methods are used to assess material attributes. Data collected during manufacturing process i.e. the combined

process measurements and other test data; serve as the basis of real time release of the final product. This would also demonstrate that each batch conforms to establish regulatory quality attributes. The real time release can be compared to alternative analytical procedures for final product release.

The Agency's approval is necessary prior to implementing real time release for products that are the subject of market applications or licenses. Process understanding, control strategies, plus on-, in-, or at-line measurement of critical attributes that relate to product quality provides a scientific risk-based approach to justify how real time quality assurance is at least equivalent to, or better than, laboratory-based testing on collected samples.

With real time quality assurance, the desired quality attributes are ensured through continuous assessment during manufacture. Data from production batches can serve to validate the process and reflect the total system design concept, essentially supporting validation with each manufacturing batch.^{4,5}

4. Strategy for Implementation

In order to enable successful implementation of PAT coordination, flexibility and communication between regulatory agency and manufacturers is very important. In the atmosphere of clear, effective and meaningful communication between the agency and industry, regulations can effectively support innovations. One such example of such exercise would be frequent meetings or informal communications.

A designated component of the PAT framework deals with uncertainties with respect to innovations and outlines broad principles for solving future scientific and technical issues. The framework directs industry in proposing and experimenting with 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:

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

Ideally the best time to implement PAT principles and tools is during the development phase. This creates opportunity to improve the mechanistic basis for establishing regulatory specifications. The recommendations provided in this guidance are intended to alleviate concerns with approval or inspection when adopting the PAT framework.

While implementing the PAT framework, industry needs to evaluate the suitability of PAT tools on experimental

and/or production equipment and processes. This can be done within the industry's quality system without prior notification to the agency. Data collected using an experimental tool should be considered research data. If research is conducted in a production facility, it should be under the facility's own quality system.^{6–9}

5. Conclusion

The ultimate goal of a PAT framework must be the implementation of robust processes with flexibility to accommodate various physical and chemical attributes of process materials by making necessary adjustment of the process conditions. The created knowledge base can be used to justify a science and risk based approach to analytical method validation and process monitoring. Significant benefits can be seen in terms of product quality in case of manufactures implementing PAT framework with the help of advance technology. Process Analytical Technology provides better knowledge of raw materials, manufacturing parameters and their impact on finished product quality. This will further translate into improved process robustness, improved quality of products, uniform dissolution results and a significant cost saving for the industry.

6. Source of Funding

None.


7. Conflict of Interest

None.

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