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Review Article

A DESCRIPTIVE REVIEW ON PROCESS ANALYTICAL TECHNOLOGY

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Abstract:

Measurement of essential process parameters that impact critical quality characteristics is at the heart of process analytical technology (PAT), which is used in the design, analysis, and control of pharmaceutical production processes. Physical and Chemical Attribute Testing (PAT) ensures high quality raw materials (i.e. at off-line, on-line, in-line). With PAT, we move away from testing the structures themselves and instead test the goods themselves at various stages of production. PAT drastically reduces the resources needed for product sampling and testing. In order to be effective, PAT must provide instruments such contemporary process analysers or analytical chemistry, endpoint process monitoring and regulating instruments, and continuous improvement and knowledge enhancement instruments. In this review, we've tried to dig into what PAT is, what it's for, what kinds of tools you can use for it, what problems it's meant to solve, how it operates, and what advantages it offers.

Keywords: PAT, Pharmaceutical, Manufacturing process, Quality assurance.

Introduction:

The term "Process Analytical Technology" (PAT) has been used to describe "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 also processes with the goal of ensuring final product quality into the product and manufacturing processes, and also continuous process improvement. "U.S. regulators have described process analytical technology (PAT) as "a method to design, evaluate, and regulate pharmaceutical manufacturing processes via the measurement of Critical Process Parameters (CPP) which impact Critical Quality Attributes (CQA)" [1-3].

The idea is to learn about the processes, identify their critical success factors (CPFs), and then monitor them in real time (ideally in-line or on-line) to improve testing efficiency, reduce unnecessary processing, improve uniformity, and cut down on wasteful rejections.

The Food and Drug Administration (FDA) has provided guidelines for the administration of PAT. According to Hinz, "the FDA attempts to incentivize the pharmaceutical business to enhance the manufacturing process" by establishing this structure. The manufacturing technology is "frozen" during the time of performing phase-2 clinical trials [1, 2] due to the stringent regulatory requirements and the lengthy development period for a new medicine.

PAT facilitates and promotes the steady improvement of industrial processes. It requires in-depth knowledge of the numerous processes involved and the use of real-time data to minimise process variance and maximise production capacity. Testing and adjusting a product in real time based on a thorough knowledge of how its many parts and processes interact is what PAT is all about. This is consistent with the guiding notion that quality in a pharmaceutical product cannot be assessed but must be deliberated into being from the outset [2, 3].

Batch processing is used extensively in traditional pharmaceutical production, with final laboratory testing performed on representative samples to guarantee product quality. This traditional method has proved fruitful in supplying the public with high-quality medications. The method fails if the end output does not meet quality standards [4]. The company will suffer a significant loss since the whole batch must be thrown away. The issue is compounded by the fact that the whole batch must be thrown out based on the outcome of the sample, even if just a small portion of it does not meet quality specifications. In other cases, the representative samples may pass the test, but the whole batch may be of inadequate quality, leading to the product being released and then recalled from shelves. Accordingly, the FDA is encouraging dialogue throughout the pharmaceutical sector about a new approach that will ease these worries. The scientific name for this kind of operation is "Process Analytical Technology" (PAT). The FDA's programme to enhance and modernise Pharmaceutical production, "Pharmaceutical Current Good Manufacturing Practices (cGMPs) for the 21st Century a Risk Based Approach," launched in August 2002, relies heavily on process analytical technology (PAT) [4, 5].

Quality-by-Design (QbD) is described in ICH Q8, Q9, and Q11, and it has become standard practise in the pharmaceutical industry for developing and producing drug substances and drug products. QbD's end result is a quality product that is both well-designed and well-understood, and which reliably maintains its function over time. A design space, (process) control strategy, and set point within the (regulatory authorised) design space

may be established using the information gained throughout development. The design space includes the materials that may be used to make a product that satisfies expectations, as well as the range of permitted modifications to that product. Analytical QbD is the name given to the use of these ideas in the creation of new analytical procedures (AQbD). Like process QbD, analytical quality by design (AQbD) seeks to create a procedure that is both well-understood and resilient, always producing the desired results as specified in the analytical target profile (ATP) [6, 7].

Objectives

It is in line with our present medication quality system that PAT seeks to understand and regulate the production process; quality cannot be tested into goods; rather, it should be built-in or by design [8-10].

Food and Drug Administration (FDA) officials realised in August 2002 that they had to do something to get people to stop being afraid to try new things, so they started a programme called "Pharmaceutical Current Good Manufacturing Practices for the 21st Century: A Risk-Based Approach." Numerous vital objectives have been set for this programme, all of which work together to increase people's ease of access to high-caliber medical treatment. The objectives are meant to guarantee that: o Modern ideas from the fields of risk management and quality systems approaches are introduced into pharmaceutical production while keeping product quality at a high standard. Manufacturers are strongly urged to take advantage of state-of-the-art scientific developments in the pharmaceutical industry.

The agency's efforts are focused on minimising the greatest threats to public health, and those efforts are well-allocated. Risks associated with subpar product or procedure quality may be evaluated and counteracted using this methodological framework based on scientific and technical concepts. These characteristics sum up the ideal scenario for the pharmaceutical industry and its oversight bodies: Methods acknowledge that it is possible to guarantee product quality and performance by planning efficient and well-thought-out production procedures.
• Mechanistic awareness of how formulation and process parameters impact product performance is the basis for product and process specification. With "real time" quality control happening constantly.
Current scientific understanding is taken into account when developing and revising applicable regulatory rules and procedures.
• Regulation based on risk,
1) The extent to which formulation and manufacturing process parameters are understood to impact product quality and performance in the scientific community. Two, the likelihood of generating a subpar product is reduced or eliminated thanks to the process control measures in place.

Insights into the Mechanisms of the PAT

In order to transition away from off-line testing, at-line testing is the initial step. This entails relocating process testing equipment to the manufacturing line so that findings may be obtained quickly. The time delays associated with transporting samples are avoided, which is a major benefit. Accelerated dissolving rate analysis and near infrared (NIR) tablet analysis are two examples of non-conventional methods for evaluating tablets, among the more commonplace dissolution, assay, friability, hardness, and thickness testing. On-line testing, which collects samples on the fly or performs periodic monitoring, is one method of process analytical chemistry. In-line testing employs probes that are in continual touch with the medication product at all times. On-line/in-line systems allow for more precise management of operations. One method that has recently gained popularity is near infrared (NIR) analysis, which may be used as a post-production or in-process measure. It is possible to see through and through solid materials since near-infrared light does not harm or react with them. PAT is not restricted to NIR but may encompass many other kinds of monitoring, such as Raman, Mid-IR, acoustic emission signals, and other imaging methods [11], despite NIR receiving the lion's share of the emphasis.

Equipment for PAT

Current and emerging technologies make it possible to design, produce, and ensure the quality of pharmaceuticals in a scientific, risk-managed manner. When integrated into a larger system, these instruments become powerful instruments for gathering data, which in turn facilitates process comprehension, the creation of risk-mitigation strategies, the attainment of continuous improvement, and the dissemination of information and expertise. These instruments may be broken down further in the PAT framework according to:

Tools for collecting and analysing data from several sources

Pharmaceutical goods and procedures are complicated multi-factoral systems from a physical, chemical, or biological standpoint. Finding the best formulation and process conditions for these systems may be accomplished via a wide variety of development approaches. The information learned via these methods of development may be utilised to determine the best possible system formulation and processing conditions. A statistical assessment of model predictions is a good way to evaluate the usefulness and accuracy of information represented by mathematical connections and models. Trials in methodology (e.g., factorial design experiments) based on the statistical concepts of orthogonality, reference distribution, and randomizations are powerful tools for detecting and investigating the influence and interaction of product and process factors. The interactions between product and process factors cannot be adequately addressed by the typical

one-factor-at-a-time experimental design. When one component does not have the same influence on the answer over a range of values for another factor, this is an example of an interaction. During the course of a product's lifecycle, the information gained from the experiments performed at various stages of development may be used as building blocks to account for an increasing level of complexity. Such organised trials provide useful data for building a product- and process-specific knowledge base. Eventually, this data may be combined with that from other development programmes to produce a comprehensive body of knowledge for the institution. This institutional knowledge base may be mined to learn valuable patterns for future development initiatives as it expands in coverage (spectrum of variables and scenarios) and data density. Process simulation models that make use of these experimental datasets may speed up development generally and aid in the process of continuous learning [12].

Technology advancements in process analytical chemistry have resulted in sophisticated process analyzers.

The need of collecting process data during production has been widely recognised during the last few decades, leading to a major expansion of the field of process analytical chemistry. Modern instruments for measuring chemical composition and physical properties have developed from more basic process measurement techniques like pH, temperature, and pressure. These cutting-edge methods of process analysis provide non-destructive tests that may reveal hidden physical and chemical characteristics of the material. The following are some possible methods for carrying out such measurements: Whereas offline research takes place in a lab, at-line testing takes place during manufacturing.

• Real-time, when a measurement device is integrated into the process via a redirected sample flow; the sample is measured and then reintroduced to the flow of the process. Measurements are taken in real time and in-line, where any disruptions to the process stream (such as probe insertion) are possible. If the sensor is not in direct touch with the substance (as in Raman spectroscopy via a window), then it does not interfere with the processing flow.

Techniques for keeping tabs on and regulating processes and their outputs

For medication formulation and manufacturing process design and optimization, the PAT framework may include the following steps: First, you need to identify and quantify the most important material and process variables that affect product quality. Plan a process measurement system that will provide on-, in-, or at-line monitoring of all important characteristics in real-time or near real-time. Third, implement process controls that allow for fine-tuning to guarantee that all relevant variables are under control. Create a quantitative link between certain features of your product and their

perceived quality taking readings of key material and process characteristics In order to effectively manage all major quality aspects, it is crucial that product design and process development be tightly coupled. For the purposes of a framework for monitoring and controlling processes, a process endpoint need not be a specific instant in time but rather the acquisition of a certain material property. Nonetheless, this does not imply that process time is irrelevant. It is important to analyse the anticipated range of process times that can be attained throughout the manufacturing phase (the process window) and to design strategies for dealing with substantial outliers. More importance should be given to process end points that will be utilised for real-time release than to those that will just be used for process control.

Four Tools for Managing Knowledge and Continually Improving

The product life cycle is a continuous learning opportunity in which data is collected and analysed continuously. With the right data, it's possible to make a case for implementing post-approval adjustments, such as incorporating cutting-edge technology. Manufacturers may benefit greatly from and make better use of approaches and IT systems that allow knowledge acquisition from such databases and scientific engagement with the regulatory body.

Methodology for Execution

According to the Agency, manufacturers' input, cooperation, and open lines of communication are all necessary for a smooth PAT rollout. The Agency is of the opinion that these methods fall within the regulatory ambit as it now stands [5]. Clear, effective, and meaningful communication between the Agency and industry, such as via meetings or informal conversations, is essential for regulations to properly encourage innovation.

The first part of the PAT framework is concerned with anticipating scientific and technological problems and providing general guidelines for dealing with them. This structure is meant to help manufacturers propose and implement new quality control and production methods. The Agency has created a regulatory approach to take such recommendations into account, and it actively promotes them. The following is part of the Agency's approach to regulation: Providing the PAT review, inspection, and compliance team with access to the latest scientific and technical information.

That which is recommended in this advice.

1. Identify

Discovering a situation where the PAT method might be useful and figuring out which aspects of quality really must be kept under tight control fall under this heading.

2. **Monitor**

When you've figured out which aspects of quality are most important, the next step is to keep an eye on them. Online instruments are often used for monitoring. Because of recent advancements in online analytical instrumentation, more parameters of interest are being monitored online. Since we can't keep tabs on something we can't control, the idea is rather straightforward. Data for the target CQA may be collected during monitoring, allowing us to assess how making changes to that CQA affects the process as a whole.

3. **Analyze**

After establishing a method for identifying and tracking essential quality points, the next step is to analyse the collected data to assess the significance of each quality indicator in terms of the process's overall success. Statistical models that might serve as definitions of the process are developed, verified, and validated at this stage. We use empirical research, engineering test designs, and historical data analysis to examine CQA's impact on the whole process [4, 13].

4. **Control**

The next phase in the PAT endeavour would be to regulate the process such that the CQA is always within defined limits once we have examined the link between the CQA and overall process effectiveness and built any statistical models. This is the single most important part of the PAT plan, since it guarantees that "real-time" quality standards will be satisfied. Report The reporting component includes any instruments that help guarantee the procedure was under control all through the processing time frame. Data may be provided in a way that improves process knowledge, and deviations from the "ideal state" can be noted in the release records thanks to reporting tools [5, 13].

Current production processes only do final product testing, when any raw material variability may be detected and corrected if necessary. It is at the development phase that all of the process factors are determined and optimised. Figure 3 illustrates how the manufacturing process is the only time when any adjustments may be made to the process variables.

Current production processes only do final product testing, when any raw material variability may be detected and corrected if necessary. During development, the values for all of the process variables are determined and optimised [14].

The Process of PAT Implementation:

Step 1

Process key parameters should be adjusted based on raw material analysis. Adjusted key factors include: Chemical characteristics, such as identity and purity. Size, shape, and degree of inter and intraparticle bonding are all examples of mechanical properties.

Step 2

Make necessary alterations to the crucial process parameters in light of essential quality features such as content uniformity, moisture content, dissolution rate, etc. In order to achieve the desired quality characteristics, such as content uniformity, moisture content, dissolution rate, etc., it is necessary to fine-tune the crucial process parameters. Different materials have different physical characteristics, thus it's important to use a combination of feed forward and backward control to account for these variations.

To see how the usage of distinct physical features and process end points may be utilised to justify and develop a strategy, we can refer to Fig. 4.

Advantages of PAT

•Decreased production costs. If standards are not reached, immediate corrective measures will be taken. Superior quality and reliability. • Compliance with rules will be simplified thanks to the use of computerised data.

Applications

Chemo metrics

The field of chemometrics combines the chemistry of chemical processes with the mathematics of massive data matrices. Due to the complexity of chemometrics, computational tools are required to do the necessary calculations. Without losing any information, these methods condense massive datasets into manageable chunks. Principal Component Analysis (PCA) and Partial Least Squares Regression are two well-applied chemo metric methods (PLS). In particular, these methods are lauded for their capacity to filter out irrelevant information, expose hidden variables, and fill in gaps in the data [1, 2].

Biological Process Assessment Technique

Bioprocess analytical technologies are those used in the research, development, scale-up, and commercial manufacture of drug substances (including intermediates, active pharmaceutical ingredients, and finished drug products) based on bioprocesses. The practical implications of PAT for the biotechnological production of medications are the subject of this paper [18].

The research team behind this project hopes to accomplish the following by learning more about the following topics: • The current technical state of the Process Analytical Technology (PAT) Initiative as it relates to pharmaceutical bioprocesses Find important participants for cooperation in Finland and throughout the world (both research and industry); Identify major existing initiatives; Survey the demands for monitoring bioprocesses for pharmaceutical manufacture; Survey the monitoring techniques and technologies available; The study's overarching objectives are to assess the current state of affairs in Bio PAT, provide suggestions for potential courses of action, establish a foundation upon which to construct future initiatives, and identify potential avenues for

financial support. Crystallization However, the initial principles of crystallisation are seldom used in the design, optimization, and control of crystallisation at production scale, making it a poorly understood unit operation. Production crystallizers have a variety of issues, such as (1) batch-to-batch irregularities in crystal size and yield and (2) a lack of consistency in the purity profile (residual impurities in crystals, or wrong polymorph or chiral purity). This article discusses common issues with industrial crystallisation, including examples, recommendations, and tactics for overcoming these challenges utilising in-situ crystallisation characterisation techniques. Process Analytical Technology (PAT) in Bioprocessing: A Case Study UPLC is used to make judgments on sample pooling throughout the chromatographic processing in real time [1, 5]. The biopharmaceutical industry is keen in adopting PAT for on-going, real-time quality monitoring. PAT has the ability to enhance management and regulation of business processes. PAT is defined as "a system for developing, evaluating, and regulating production via timely measurements (i.e. during processing) of essential quality and performance characteristics of raw and in-process materials and processes, with the purpose of assuring end product quality." One of the aims of the PAT framework is to establish and perfect procedures that reliably provide a specified final product quality every time production is completed.(24) The three main criteria for determining whether a process is well understood are whether or not (1) all critical sources of variability have been identified and explained; (2) variability is managed by the process; and (3) product quality attributes can be accurately and reliably predicted over the ranges of acceptance criteria established for materials used, process parameters, manufacturing conditions, and other conditions. Infra-red light Powder flow, dissolving rate, compressibility, and tablet hardness are only some of the physical attributes that are affected by the particle size of a powdered granulation mix or powdered pharmaceutical raw material.(25) Clarke came to the conclusion that near-infrared microscopy (NIR) was an effective method for analysing the sample's chemical components, including their particle form, particle dispersion, and cluster size. Method of Raman Rays spectroscopy has been utilised to keep tabs on API moisture levels. Digital still camera with charge-coupled device Wotan et al. used an image probe to measure particle size along a high-throughput granulator line.(20) To avoid excessive granule formation in the high shear granulator, an image probe and fuzzy logic control system were used. Accurate and consistent granules production was possible under the system's control. A fluidized-bed granulation method was evaluated by Lateen et al. utilising a monochromatic CCD camera to measure particle size increase. Growth and granulation, two final stages of the fluidized bed granulation process, may be analysed in real time using at-line sample analysis. (21)The imaging method utilised yielded fast changes in granule particle size, the researchers concluded [12]. The synthesis endpoint may be determined in real time

by separating mono- and bi-salts using FT-IR ATR. Better efficiency is the result of better quality control, greater yields, and the elimination of the technique transfer across labs using different FT-IR equipment (15, 16, 19).

Conclusion

There are several ways in which the pharmaceutical sector may profit from the use of process analytical technologies. Raw material physical and chemical characteristics, as well as an understanding of production factors, are all improved with the information provided by PAT, which has a direct bearing on the quality of the final product. When used together, these factors strengthen the process, improve the product, enhance process control, and shave off significant amounts of time, all of which save money and help establish a distinct identity for the company.(23)

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