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A REVIEW ON APPLICATION OF PROCESS ANALYTICAL TECHNOLOGY (PAT)

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ABSTRACT

The initiative titled "Pharmaceutical Current Good Manufacturing Practices (CGMPs) for the 21st Century—A Risk-Based Approach," launched by the FDA in August 2002, aimed to modernize and improve pharmaceutical manufacturing processes, encouraging the adoption of Process Analytical Technology (PAT) within the industry. PAT offers significant potential for enhanced operational control and regulatory compliance through continuous real-time quality assurance. Over the past decade, extensive research and development have been conducted by both academic and industrial contributors on this subject. This paper begins with a concise overview of the evolution of PAT concepts and explores their broader application within the pharmaceutical industry. The focus then shifts to PAT applications in biotech processes, with particular attention to developments over the last five years. While there has been substantial progress in the ability to analyze and monitor critical process and quality attributes in the biotech industry, further advancements are needed in utilizing this data for process control, optimizing yield, and ensuring product quality. Achieving these outcomes is essential to fully realize the benefits of PAT implementation.

KEYWORDS: *Process Analytical Technology (PAT), PAT Goals, PAT Framework, What is PAT, PAT Application In Chemical Industries, PAT Application In The Pharmaceutical Industry, PAT Appllication In The Biotechnology Industry.*

INTRODUCTION

Process Analytical Technology (PAT) encourages the voluntary development and implementation of innovative approaches to pharmaceutical development, manufacturing, and quality assurance. The scientific, risk-bas*-d framework of PAT is designed to promote innovation and enhance efficiency in these areas. This framework is built on a thorough understanding of the manufacturing process, which facilitates innovation and allows for risk-based regulatory decisions by both the industry and regulatory agencies. It comprises two key components: (a) a set of scientific principles and tools that support innovation, and (b) a regulatory strategy designed to accommodate and encourage such innovation.

The regulatory strategy includes a PAT team approach for Chemistry, Manufacturing, and Control (CMC) review, as well as for current good manufacturing practice (CGMP) inspections. It also involves joint training and certification for PAT review and inspection staff, ensuring a consistent and knowledgeable approach to regulatory oversight.

Traditionally, pharmaceutical manufacturing has relied on batch processing, where laboratory testing is conducted on collected samples to assess quality. While this approach has been effective in delivering safe and reliable pharmaceuticals, there are now significant opportunities for improvement through innovation in product development, process analysis, and control.

Despite these opportunities, the pharmaceutical industry has often been reluctant to adopt innovative manufacturing systems. One frequently cited reason is regulatory uncertainty, which arises from the perception that the current regulatory framework is rigid and not conducive to innovation. For instance, many manufacturing processes are seen as static, with any changes requiring regulatory submissions. Additionally, other scientific and technical challenges have contributed to this hesitancy.

As pharmaceuticals play an increasingly vital role in healthcare, the manufacturing sector must evolve by integrating innovation, cutting-edge scientific and engineering knowledge, and advanced quality management practices. This will enable the industry to meet the challenges posed by new discoveries, such as novel drugs and nanotechnology, as well as emerging trends like personalized medicine and genetically tailored treatments.

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PAT Goals

The US FDA introduced an initiative titled "Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach." This initiative aims to enhance the American public's access to high-quality healthcare services by modernizing pharmaceutical manufacturing practices. Its goals are designed to achieve the following:

Ensure that the most up-to-date risk management and quality systems approaches are integrated into pharmaceutical manufacturing, while maintaining product quality.

Encourage manufacturers to adopt the latest scientific advancements in pharmaceutical manufacturing and technology.

Facilitate a coordinated and synergistic operation between the agency's submission review and inspection programs.

Promote consistent application of regulations and manufacturing standards by both the agency and manufacturers.

Support innovation in pharmaceutical manufacturing through the agency's risk-based management approach.

Optimize the use of agency resources to efficiently address the most significant health risks.

This approach is grounded in science and engineering principles for assessing and mitigating risks related to poor product and process quality. The desired state of pharmaceutical manufacturing and regulation is characterized by the following:

Product quality and performance are ensured through the design of effective and efficient manufacturing processes.

Product and process specifications are developed based on a mechanistic understanding of how formulation and process factors influence product performance.

Continuous, real-time quality assurance is implemented.

Regulatory policies and procedures are adapted to reflect the most current scientific knowledge.

Risk-based regulatory approaches take into account:

1. The level of scientific understanding regarding how formulation and manufacturing process factors affect product quality and performance.
2. The capability of process control strategies to prevent or reduce the risk of producing poor-quality products.

PAT Framework

Quality is built into pharmaceutical products through a thorough understanding of several critical factors, including:

The intended therapeutic goals, the patient population, the route of administration, and the drug's pharmacological, toxicological, and pharmacokinetic profiles

The chemical, physical, and biopharmaceutical properties of the drug.

Product design and the selection of components and packaging based on the drug's attributes.

The design of manufacturing processes using principles from engineering, material science, and quality assurance to ensure consistent and reproducible product quality and performance throughout the product's shelf life.

Effective innovation in drug development, manufacturing, and quality assurance should address key questions, such as:

What are the mechanisms of drug degradation, release, and absorption?

How do product components influence quality?

Which sources of variability are critical to control?

How does the manufacturing process handle variability?

A key objective of the PAT framework is to design and develop well-understood processes that consistently deliver a predefined level of quality at the end of production. Improvements in quality, safety, and efficiency will vary based on the specific process and product, and may include:

Reducing production cycle times through on-line, in-line, and at-line measurements and controls.

Preventing rejects, waste, and reprocessing.

Enabling real-time product release.

Increasing automation to enhance operator safety and reduce human error.

Optimizing the use of energy and materials while increasing production capacity.

Supporting continuous processing to improve efficiency and control variability.

What is PAT

Process Analytical Technology (PAT) is defined as "a system for designing, analyzing, and controlling manufacturing processes through timely measurements (i.e., during processing) of critical quality and performance attributes of raw materials, in-process materials, and final products, with the goal of ensuring product quality." The main objective of PAT is to develop well-understood processes that consistently deliver a predefined level of quality at the end of manufacturing. A process is considered well understood when:

1. All critical sources of variability are identified and explained.
2. Variability is controlled by the process itself.
3. Product quality attributes can be accurately predicted under defined conditions, including materials, process parameters, and environmental factors.

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PAT implementation aims to achieve one or more of the following
Enhanced process understanding.
Improved yields by preventing scrap, rejects, and reprocessing.
Reduced production cycle times through in-line, on-line, or at-line measurements and control.
Lower energy consumption and increased efficiency through the transition from batch to continuous processes.
Cost reduction through minimized waste and energy usage.
Real-time release of product batches.
From an implementation perspective, PAT can be seen as a three-step process:
1. Design Phase: This phase begins during process development, when unit operations are being designed, optimized, and characterized. Critical Quality Attributes (CQA) and Critical Process Parameters (CPP) are identified, which influence the CQAs. Understanding these is key for the next phases of PAT.
2. Analyze Phase: In this phase, suitable analyzers are identified to monitor CQAs and CPPs. PAT applications can occur in various modes:
At-line: Samples are removed and analyzed close to the process stream.
On-line: Samples are removed for analysis and then returned to the process.
In-line: Samples are analyzed without removal.
Off-line: Samples are removed and analyzed away from the process stream.
For effective PAT, analytical results must be available quickly enough to support real-time decision-making.
3. Control Phase: This phase involves designing control strategies based on process understanding, allowing data from the analyzers to be used for real-time process adjustments, ensuring consistent performance and product quality.

PAT goes beyond just analysis. For example, in biotech processes, UV absorbance at 280 nm is often used to monitor chromatography columns separating products from impurities such as host-cell proteins (HCP). If the product and HCP are well-separated, UV absorbance can effectively guide consistent product pooling, as shown in Fig. 1 However, if the separation is poor (as in Fig. 1), UV absorbance alone may not be suitable for PAT, as it could lead to inconsistent product quality due to variable HCP levels.
In essence, PAT ensures that the manufacturing process is continuously monitored and controlled to maintain high product quality, leveraging advanced analytical tools and real-time data to drive informed process decisions.

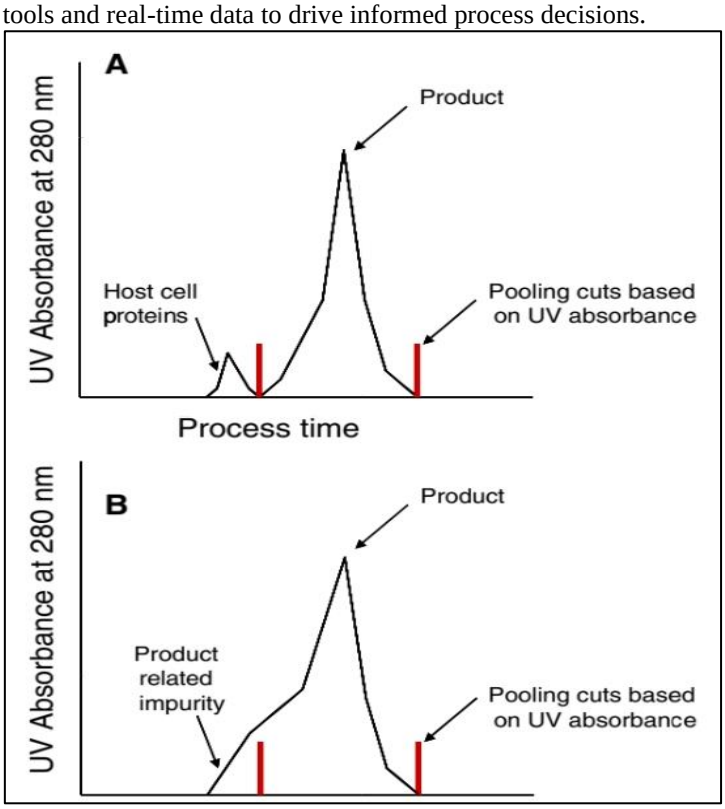

Fig. 1 Use of UV absorbance at 280 nm for pooling of fractions from a process chromatography column separating a protein product from other host cell proteins. A. Baseline separation of product from HCP. B. Incomplete separation of product from HCP

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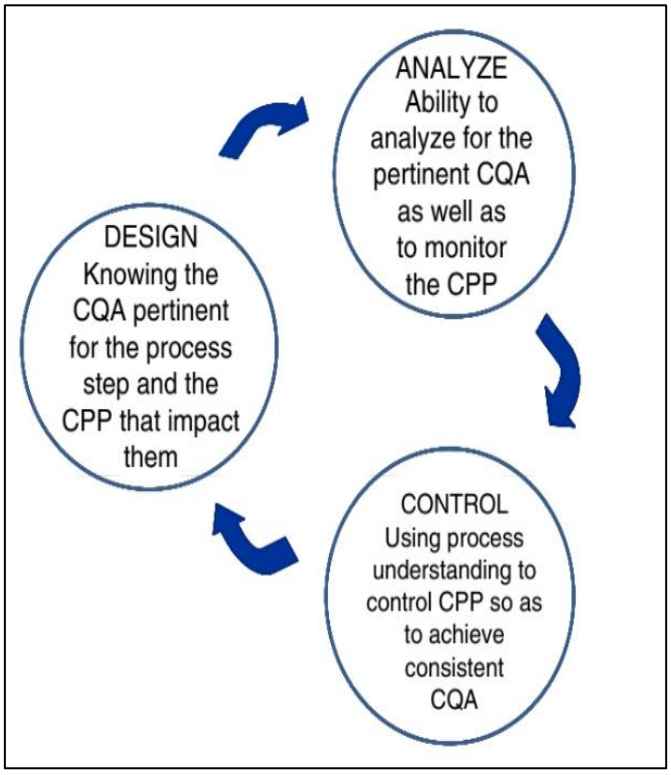

Fig. 1.1 The three steps that must be taken for PAT implementation, and the objective of each step

PAT Application In Chemical Industries

The The concept of Process Analytical Technology (PAT) has been applied in the chemical industry for several decades and has been extensively reviewed in various publications. Over time, the industry has adopted process analyzers and modeling techniques that not only optimize productivity and product quality but also provide real-time assurance of process control. In the event of deviations, these tools suggest corrective measures to bring the process back under control. Table 1 summarizes some recent applications of PAT in the chemical industry.

Common process analyzers used in these applications include Near Infrared (NIR) spectroscopy, acoustic sensors, nuclear magnetic resonance (NMR), Raman spectroscopy, attenuated total reflectance (ATR), and Fourier transform infrared spectroscopy (FTIR). To analyze and model the large amounts of data generated by these analyzers, statistical methods such as Process Component Analysis (PCA), Partial Least Squares (PLS), and Soft Independent Modeling of Class Analogy (SIMCA) are employed.

NIR and Mid Infrared (MIR) spectroscopy, for instance, have been proposed as tools for predicting the quality of diesel/biodiesel blends by evaluating parameters such as density, sulfur content, and distillation temperatures. These methods have demonstrated performance comparable to traditional, more labor-intensive techniques. NIR has also been utilized as an analyzer to assess the effects of various operating conditions on the recovery, selectivity, and productivity in the production of methyl isobutyl ketone (MIBK). This PAT approach allowed for more time-efficient experimentation, resulting in a 30% increase in MIBK productivity.Additionally, NIR, combined with appropriate statistical tools, has been applied in raw material analysis, product quality measurement, and process monitoring.

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Table 1 Example Of PAT Application In The Chemical Industry

Application	Process Analyzer	Statistical Tool	Obervation
Rapid and accurate tablet identification	Acoustic resonance Spectroscopy	Partial least-squares (PLS) calibration	NIR and MIR spectra have been shown to help in predicting distillation temperature and sulfur content of diesel or biodiesel
On-line determination and control of the water content of a continuous conversion Reactor	NIR	PLS with distributed control system	On-line process control led to significant improvement in yield
Simultaneous determination of methanol and ethanol in gasoline	NIR	PSL	Non-destructive and non-polluting method of analysis enables faster detection of methanol adulteration of the gasoline
Simultaneous monitoring of solute concentration and polymorphic state of the crystal	Raman spectroscopy and attenuated total reflectance (ATR) Fourier transform infrared (FTIR) spectroscopy	PLS	PAT approach was utilized to understand how the feeding strategy for the reactant affects the polymorph composition of L-glutamic acid
Analysis of the organic content of waste water	Nuclear magnetic resonance (NMR) spectroscopy	PLS	Less time-consuming and the cost-effective method for analysis of organic content
Catalysis reaction involving conversion of acetone to methyl isobutyl ketone (MIBK)	In-line NIR	Design of experiments (DOE), Principle components analysis (PCA), PLS, and cluster analysis	PAT application helped in determination of the factors affecting the productivity, selectivity, and yield of the MIBK and thereby leading to improved productivity for MIBK
Industrial process for granulation of urea during fertilizer production	Acoustic sensor with high temperature microphone probe	PCA and PLS PAT	PAT approach used to predict fluidization airflow, reflux of fines to the reactor, granule moisture content, and granule size
Raw material identification and quality control	NIR	K nearest neighbor (KNN) and soft independent modeling of the class analogy (SIMCA)	Fast and cost-effective method for raw material analysis

PAT Application In The Pharmaceutical Industry

The nnovations in process analytical chemistry and advancements in data capture and analysis have been key drivers in the adoption of Process Analytical Technology (PAT) within the pharmaceutical industry. The main feature of PAT is that it integrates quality

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into the product during the manufacturing process, rather than testing for quality after production. The PAT framework combines risk management with at-line and on-line sensors to monitor, control, and design processes while predicting process performance. Various analytical techniques are used in the pharmaceutical industry, such as Fourier transform infrared spectroscopy (FTIR), UV-spectroscopy, gas chromatography, high-performance liquid chromatography (HPLC), X-ray diffraction spectroscopy, and near-infrared (NIR) spectroscopy.

In a typical tablet manufacturing process, PAT approaches can be applied to different stages of production, including dispensing, blending, milling, compression, and tablet coating. For instance:
NIR spectroscopy is used to quickly and reliably test raw material quality, ensuring that only raw materials that meet specifications are used in the process.
In-line temperature monitoring during extrusion can be controlled through feedback loops connected to the heating/cooling system.
Particle-size distribution can be continuously monitored during milling to ensure process consistency, with control provided via feedback or feed-forward mechanisms
At-line testing of weight, thickness, potency, and hardness can be conducted at the tablet press, allowing for continuous quality verification and feedback control during compression.
This approach not only enhances process understanding but also improves process control.
Recent PAT applications in the pharmaceutical industry have focused on a range of technologies. NIR is widely used for applications like determining active ingredient content, characterizing powder flow, analyzing raw materials, and measuring dissolution rates. Other analytical tools include acoustic resonance spectroscopy, terahertz pulsed spectroscopy, and laser-induced breakdown spectroscopy. These tools demonstrate the increasing capability to design processes where each step is continuously monitored and controlled to ensure it performs as expected.
While significant progress has been made, using analyzer data to adjust operating conditions and maintain process control remains relatively rare. Developing such control schemes is expected to be a key focus of the pharmaceutical industry in the future.

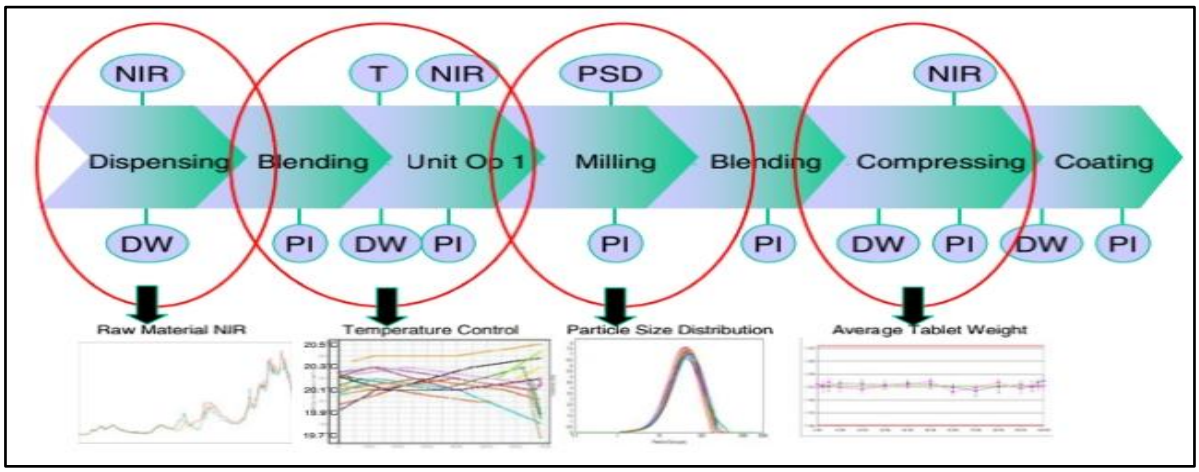

Fig:-2 The different unit operations that comprise a typical pharmaceutical process.

Table 2: Examples of PAT applications in the pharmaceutical industry

Application	Process Analyzer	Statistical Tool	Obervation
Rapid and accurate 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 mislabeling of drug
Quantification of the active ingredient in pharmaceutical injectable formulations	NIR and UV–visible Spectroscopy	PLS	More ecoomical and less time-consuming method for quantification of the lysine clonixinate
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

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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
Active determination of content of uncoated pharmaceutical Pellets	NIR	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.

PAT Appllication In The Biotechnology Industry

The /Figure 3 illustrates a typical process for producing a biotech product, highlighting some of the major unit operations involved. While the earlier discussion on implementing PAT in the chemical and pharmaceutical industries is also relevant to biotechnology, there are unique considerations that arise with biotech processes and products These include:

1. Proteins, the primary products in biotechnology, are large, complex, and heterogeneous molecules.
2. Biotech processes are significantly more complex than typical chemical or small-molecule drug manufacturing processes in terms of the number of batch records, product quality tests, critical process steps, and the quantity and complexity of generated process data .
3. Protein products are highly sensitive to the manufacturing process used in their production. Lot-to-lot variability in product quality is common, even when the same process is followed. Additionally, variability in raw materials can also impact product quality .
4. The raw materials used in biotech manufacturing are complex and prone to lot-to-lot variability .
5. Our understanding of the relationship between each product's quality attributes and the clinical safety and efficacy of the drug is generally limited

Due to these factors, implementing PAT for biotech processes is more challenging Table 3 and Figure 5 help illustrate these challenges. Table 3 presents key biotech unit operations, their typical process times, important quality or process attributes, analytical methods for measuring these attributes, analysis times, and the ratio of available decision-making time to analysis time. Figure 5 visualizes how this ratio changes across different unit operations.

The ease of implementing PAT in a given operation can often be gauged by this ratio. For example, processes like mammalian cell culture, where decision-making time is ample and sample analysis can be done without rushing, allow relatively straightforward PAT implementation. On the other hand, for operations like process chromatography, where the available decision-making time is shorter than the analysis time, successful PAT implementation may require adjustments in process design, equipment, or analytical methods

In this review, we will categorize the process into four main parts: upstream, harvest, downstream, and formulation. In the following sections, we will examine PAT applications in each of these areas. We will also discuss the role of PAT in chemometrics.

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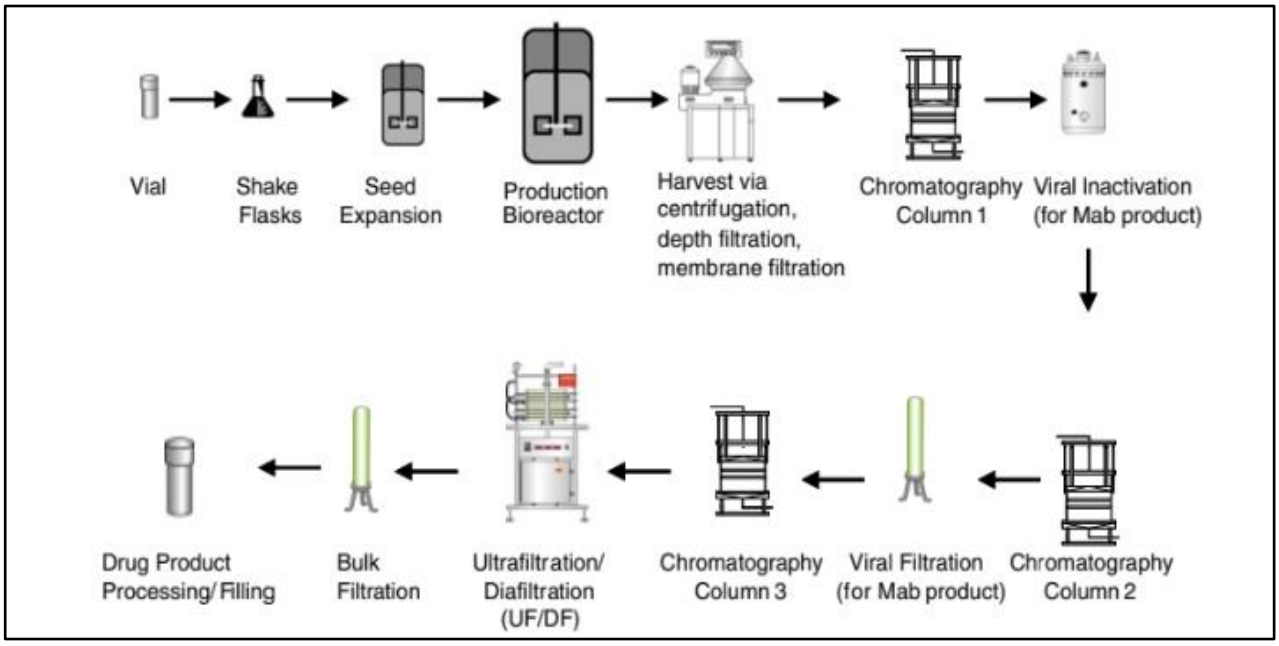

Fig. 3 A typical production process for a biotech product

Table 3 : Illustration of the challenges of executing PAT for biotech processesIllustration of the challenges of executing PAT for biotech processes.

Process Segment	Major process steps	Typical process time, tp (hrs)	Typical decision time, td (hrs)	Quality Attribute (QA) or Process Attribute (PA)	Analytical Method	Typical analysis, ta (hrs)	Ratio (td/ta)
Upstream	Microbial fermentation (production)	24	2	Misncorporation	HPLC	1	2
	Mammalian cell culture (production)	240	10	Glycosylation	Oligosaccharide profile	1	10
Downstream	Refolding	20	2	Misfolds	HPLC	0.5	4
	Chromatography	8	0.5	Aggregation	HPLC	1	0.5
Harvest	Certrifugation	8	1	Recovery	HPLC	1	1

CONCLUSIONS

1. Enhanced Process Understanding and Control: PAT technologies have demonstrated their capacity to significantly improve process understanding by providing real-time insights into critical quality attributes (CQAs) and critical process parameters (CPPs). This enables industries to achieve consistent product quality through improved process control.
2. Reduction in Production Costs and Time: With the application of PAT, companies can achieve faster production cycles, reduce waste, and minimize the need for post-process testing. The reduction in rework and scrap due to real-time adjustments based on PAT data leads to lower costs and a more efficient workflow.
3. Regulatory Compliance and Quality Assurance: PAT aligns closely with regulatory guidelines (e.g., from the FDA) that promote quality-by-design (QbD) principles. By integrating PAT, companies can meet compliance requirements more effectively while enhancing quality assurance throughout the production cycle.
4. Applications Across Industries: While PAT originated in the pharmaceutical industry, its applications have expanded into sectors like biotechnology, food processing, and chemicals. This versatility underscores PAT's adaptability in different manufacturing contexts, which is driving broader industry adoption.
5. Challenges and Future Directions: Despite its benefits, the adoption of PAT is challenged by high implementation costs, the need for skilled personnel, and data integration issues. Future directions may focus on developing cost-effective PAT tools, better data management systems, and advanced modeling techniques to support real-time decision-making.

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6. Overall Impact and Future Prospects: The integration of PAT represents a shift towards smarter, more sustainable manufacturing practices. As technology advances and industry experience grows, PAT is expected to play an increasingly central role in optimizing manufacturing, ensuring quality, and meeting industry demands for efficiency and regulatory adherence.

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