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Review Article

Overview: flexible and versatile approach of quality by design & process analytical technology in industries

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ABSTRACT

Quality by Design (QbD) is crucial to the creation of contemporary in pharmaceuticals, microbiology, biotechnology, product management etc. In order to build proactive, scientific, and risk-based processes and products, QbD helps and supports both the industry and the FDA. Instead of waiting until the final quality check of the finished product, it is founded on the idea of establishing quality from the very beginning of the process. A successful plan that lowers batch failures and recalls is finally provided by an efficient QbD approach, which offers insights and crucial upstream information throughout the development process. The purpose of this review is to provide an overview of the implementation of Quality by Design (QbD), its tools, elements, and techniques, the relevancy with various guidelines, and the use in present-day pharmaceutical. The IQ Consortium provides information on the current situation of process analytical technology (PAT) as it relates to the creation of active pharmaceutical ingredients (API) in branded pharmaceutical firms. The article gives concrete examples of why and how the pharmaceutical industry uses PAT tools in API development by using an API process pipeline. PAT can reduce personnel risks involved with sampling dangerous compounds for in-process testing and increase R&D efficiency. Although not all chemical processes or stages are easily suited to applying the features of the PAT toolbox, PAT permits accurate and speedy (real or near time) evaluations of processes that might involve compounds that are highly dangerous, transitory, or heterogeneous when necessary. The major regulatory agencies and the biotech sector have worked hard to assist the application of the ideas of Quality by Design (QbD) and Process Analytical Technology (PAT) over the past ten years, with varying degrees of success. Despite the fact that just one biotech therapy has received approval under the QbD paradigm thus far, the tools and methods associated with these two ideas are deeply ingrained in the work procedures of the majority of international pharmaceutical firms. This overview is mainly focused on the QbD and PAT's development in the first place. Second, give an overview of QbD and PAT implementation and point out any places where more contributions are possible.

1. Introduction

In order to ensure the quality of the end product, PAT is described as "a system for designing, analysing, and controlling manufacturing through timely measurements

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(i.e., during processing) of critical quality and performance attributes of raw and in-process materials and processes.".[1] The focus of the global pharmaceutical industry is currently changing. With significant ramifications for the direction of science in R&D, the impact of patent expirations, low R&D productivity, and pricing pressure from conventional payers in established markets have changed big Pharma strategy. However, the need for pharmaceuticals continues to expand noticeably, with an increased focus on developing markets like those in Asia and Latin America. The focus of research is shifting away from cures for large subpopulations and towards treatments for niche markets. These two tendencies will increase supply chain complexity and diversity, which will make them more and more necessary to have a larger worldwide presence.[2] In order to stay up with these anticipated developments, manufacturing science must advance. Along with robust products and processes that are scaleable, easily transferable between sites, and relatively insensitive to changes in environmental conditions and raw material supply, lean and agile supply chains that can handle diverse product portfolios with frequent variations in demand will be needed. In this regard, the fundamentals of Quality by Design (QbD) and quality risk management (ICH Q8, Q9, and Q10), which have historically been supported by senior figures in the regulatory field, have a crucial role to play in ensuring that those in need receive access to safe and effective medicines (Pharmaceutical cGMPs for the 21st century - A risk-based approach). Additionally, emerging manufacturing technique will need to be implemented along with related control mechanisms, which will be crucial for producing complex goods like biopharmaceuticals and novel drug delivery systems. Therefore, significant infrastructural investment is required, coupled with crucial expansions of the related competence and skill base in business, academia, and the health agencies. We have picked four areas where scientific knowledge is either absent or insufficient but which we believe have the potential to be of significant future use to society.[3]

The development of products for personalised healthcare, continuous processing in the production of pharmaceutical products, quantitative quality risk estimation for pharmaceutical development, including life cycle management, and downstream handling of biopharmaceutical products are some of the scientific themes undergirding QbD and PAT. Each of the four categories is briefly described in this document, which also emphasises the areas that need widespread support in order to promote science and create a strong talent base for businesses, universities, and health organisations.[4–6] The International Consortium for Innovation & Quality in Pharmaceutical Development members provide an overview of the current situation of process analytical technologies (PAT) in the pharmaceutical sector. PAT (also known as in situ analytics) technologies are widely used in pharmaceutical processes to support the development, scale-up, and production of pharmacological substances and dosage forms.1−4 Even at this point, the FDA's full vision of PAT, which it defines as "a system for designing, analysing, and monitoring production through timely metrics (i.e., during processing) of critical performance and quality attributes of raw and in-process supplies and procedures, with the goal of ensuring final product quality"5, has not been fully realised by the industry for a significant amount of products on the market or in development. The necessity for industry to realise this PAT objective is hotly argued in organisations, conferences, and online forums. Regardless of the type or location of the data analytics and controls, or whether additional cost benefits could be realised using in situ analytics and real-time control, the industry identifies and implements controls.[7]

2. Implementation of Pat

To guarantee that the entire QbD process was successful, appropriate analytical approaches are crucial. Since the Food and Drug Administration (FDA) published the PAT guideline in 2004, the pharmaceutical industry's research and innovation have switched their attention to the creation of real-time analysis throughout production processes. It is well understood that a solid-state examination of a medicine cannot be done solely at the conclusion of the manufacturing process. The three steps of design, analysis, and control are necessary for a successful PAT implementation, as has been noted in the literature. To determine which quality attributes are relevant to a specific unit activity and which procedure variables and raw material characteristics have the greatest influence, experimentation is carried out during the design step. Using this information, it is then possible to pinpoint the qualities, process variables, and raw material characteristics that should be taken into account when designing an efficient PAT-based management strategy for the process. In the analyse step, a suitable analytical instrument is chosen to analyse the selected quality characteristic, as well as the selected process parameters and the attributes of the raw materials, if necessary. In order to determine what steps to take if the process productivity deviates from the ideal course, the control phase comprises assimilation of the information gathered from analysis into a suitable control scheme. Regulatory bodies urge users to use PAT technologies as much as feasible when creating NDAs and ANDAs. Utilising the improved process knowledge attained through the use of PAT tools, the design of both products and processes can be improved, leading to the creation of goods with optimised quality attributes and decreased risks for producers and consumers. In addition, PAT tools can provide significant cost savings by cutting down on operation time, invasive analytical examination, and waste disposal. On this subject, thorough reviews have

already been written.[8]

3. What is Pat

"Analysing" in the FDA's PAT definition refers to in-situ analytical tools, which cover a wide range of measurement and instrument types, including thermocouple, pH probe, vibrational spectroscopy (mid-infrared, near-infrared, Raman, ultraviolet), mass spectrometry, chromatography, focused beam reflectance measurement, and nuclear magnetic resonance. There is no one in situ analytical instrument that will work for all applications, just as there is no one off-line analytical tool that can satisfy all process development knowledge or control strategy needs for a product. In fact, using in situ tools for some types of chemistry can be difficult at best, necessitating sampling and off-line testing.

As a result, when choosing which analytics are suitable for both process and outcome knowledge, monitoring, and control, PAT tools are simply one set of methods for analysis to take into account. Based on the chemistry, stage of development, method availability (both while being developed and at the manufacturing site), process instruments accessibility and arrangement, personnel expertise in the technique, and regulatory acceptability, the suitable analytical techniques for the process or product are chosen.[9]

4. Why Use Pat

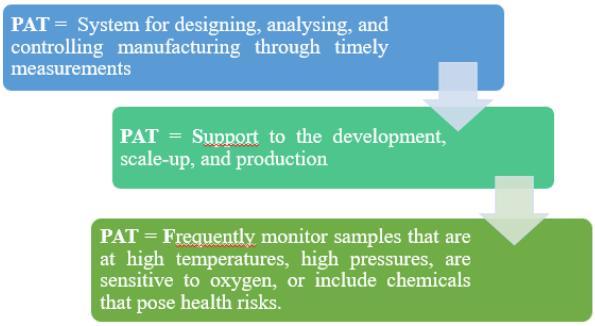

Figure 1: Applicability of PAT analysis

undesirable to obtain using conventional off-line approaches (such as transitory intermediates, highly hazardous compounds, high pressure systems, high or low thermal systems, and heterogeneous systems).[9,10]The capacity to determine process components with a minimal amount of disruption is one of the biggest obstacles to comprehending complicated physical and chemical processes. The measurement is the cornerstone of PAT, whether it is used in R&D or manufacturing.chemometric predictive models. The intended result of these predictive models, which can be both quantitative and qualitative in character, is to forecast process outcomes.[10]utilised from preclinical to commercial production phases of development and is a useful collection of analytical tools for the bio pharmaceutical scientist to investigate processes. The analytics required to provide an understanding and characterization of the procedure may be complicated in the early stages of development. The use of multivariate analyzers enables researchers to track the emergence and development of many process components. The number of parameters thought to be crucial can be decreased as the process is described and understanding can be acquired through these measurements. The goal is to reduce the complexity of the control and monitoring technology as much as is practicable as the process gets closer to production ready and the process parameter limits for control are set. To control the process, the outcomes of advanced PAT are best used in conjunction with straightforward manufacturing data.[9–11]

5. Process Understanding and Control

A better knowledge of the chemical and manufacturing process through the application of PAT results in the development of robuster chemical processes while utilizing crucial resources like as research people and equipment more efficiently. Furthermore, PAT tools can be used to bridge multiple reaction scales and analyse the reaction in real time. Mixing variations may occur when scaling up to experimental and industrial scales from lab scale. Mass transfer and heat exchange, particularly in heterogeneous processes, can be critical to process performance as well as safety.[11,12]A common rule of thumb for risk-based method development is that thermodynamically managed procedures scale up reliably, but kinetically controlled processes require more scrutiny during the scaling process. Furthermore, technologies that are mass transfer or heat transfer rate-limited should be scrutinized more closely. When PAT is brought to production, it can be used in two ways: process control or ongoing process understanding. The term "process control" indicates technological equipment and methodology will be employed in decision-making and, as such, must be GMP compliant. It means the current effort focuses on process comprehension; a follow-up study on the use of PAT tools for control of processes in a GMP manufacturing setting will be created. PAT is merely an additional set of analytical procedures that come into interaction with the process through a probe. When using development mode samples to generate process information, the materials of probe design must be addressed.[11]

6. Safety

PAT tools play a critical role in enhancing both process and product safety. To verify that the reaction proceeds within predetermined bounds and maintain product safety, in situ testing can be employed to provide fast process measurements. Additionally, these same techniques are employed to reduce worker exposure to dangerous contaminants during sampling. Any industrial production organization's top priority is to eliminate process dangers that could have a negative impact on the community, the workforce, and process equipment.[11,12] By getting time-varying evaluations of potentially hazardous compounds and events and then using sound reaction principles of engineering to limit the risk, numerous process risks are avoided in the pharmaceutical sector. The measurements are often carried out in a laboratory, and the knowledge acquired is used to estimate worst-case scenarios along with process models. After creating the necessary circumstances for the process to run safely, a plan is created to make sure it stays within that safe operating range. Simpler methods that have been shown to offer information suggestive of the variables to be regulated may replace the PAT tests that provide extensive understanding in the lab. However, more sophisticated PAT may be implemented for real-time measurements in the production process depending on the risk. PAT is a very effective method for guaranteeing that chemical reactions are carefully monitored and proceed according to specifications. It also has the advantage of removing risks for workers who might have to sample potentially dangerous compounds for in-process testing. PAT can frequently be used safely to monitor samples that are at high temperatures, high pressures, are sensitive to oxygen, or include chemicals that pose health risks.[10–12]

Understanding the dynamics of every component's operation during the synthesis of clinical development therapeutic substances can also help maximise output and throughput while reducing process-related impurity generation and procedure material holding durations. In these situations, PAT may be utilised as an in-process control (IPC) technique, as a predictor that an off-line IPC test would be successful, ensuring a constant batch cycle time, or to analyse the process on a broader scale.[12]

7. When to Use Pat

Throughout the entire process of developing a medication, in situ insights may be applied. These instruments are frequently used for process development and understanding in the research, preclinical, and initially clinical phases. As the programme progresses through the clinical phases and into commercial manufacture, as described in the preceding section, the value when using the tools and how the technologies are used can vary dramatically. Physical heterogeneity is prevalent in many pharmaceutical manufacturing processes. The advantages of continuous processing over batch processing for scale-up include the ability to run energetic chemistries safely, the quick growth of discovery chemistry for supplying first toxicological research, and potential faster process development duration. The capacity to quickly alter process variables (as opposed to running a new batch for every change and assessing the effects on the produced material) accounts for the shorter development time. PAT must be used in these processes to show that they are in steady state, to serve as in-process controls, and maybe as parametric release methods.[12,13]

8. Pat Applications

Identification of the raw material. Before using raw materials in a manufacturing process, it is important to verify their identification both when they are received and before. Traditionally, spectroscopic techniques (such IR) and comparing to a standard are used to carry out this identification in the lab. This approach can be time- and resource-consuming yet being effective. Recently, improvements in the functionality and quality of miniature spectrometers have made it possible to create portable devices that can do identity checking in warehouses.[12,13] Many of these portable equipment can gather high-quality spectra through transparent containers (like glass or polyethylene) without sampling the material. The specimen spectrum is contrasted to a built-and-stored standard spectrum inside the instrument for identity assessment and conformity. The detection of fake pharmaceuticals also frequently uses these tools. Due to its great specificity and simplicity of sample presentation, Raman spectroscopy is an especially popular technique, while NIR and MIR devices are also available and suitable for some applications. On this subject, more recent articles with greater detail have been written. Therefore, effective monitoring, management, and knowledge of chemical responses can be crucial to ensuring the smooth functioning of a process. In a conventional reaction evaluation, the combination is sampled at predetermined intervals; the collected samples are then handled and subjected to an off-line procedure, often based on chromatography, for manipulation and analysis. This method does provide a glimpse into the reaction's profile, but it does not provide a real-time profile. Real-time reaction monitoring is compatible with different PAT techniques, and the best technology will be chosen based on a variety of parameters. Examples of a variety of various reaction monitoring technologies will be discussed in this section.[12–14]

The transformation of an enantiomerically pure starting material into an enantiomerically pure product serves as a good illustration of this. Nuclear Magnetic Resonance Spectroscopy in real time. Online NMR (nuclear magnetic resonance) spectroscopy includes feeding a reaction mixture from a reaction vessel to the NMR in a continuous,

recirculating stream. The development of the reaction is subsequently followed by the regular recording of NMR spectra. The intrinsic quantitative nature of NMR, the lack of sample isolation or manipulation, and in situ structural characterisation of intermediates that would not survive isolation from the reaction mixture are all benefits of this approach.[15]

9. Quality By Design (QbD)

The quality pioneer Dr. Joseph M. Juran created the idea of quality by design (QbD). According to Dr. Juran, quality should be built into a product from the start, and the majority of quality crises and issues stem from poor product design. According to Woodcock, a high-quality drug product is one that is free of contamination and consistently provides the consumer with the therapeutic benefit stated on the label. The US Food and Drug Administration (FDA) promotes the use of risk-based strategies and QbD principles in the development, production, and regulation of pharmaceutical products.[16] High level guidelines about the scope and definition of QbD as it relates to the pharmaceutical business are provided in these documents. In spite of this, many guidelines and publications do not go into great length about implementation. Despite recent publications, regulators, academics, and industry scientists are still unclear. This essay aims to illustrate the goals of pharmaceutical quality-by-design, in addition to outlining its theory, components, and instruments for execution.[16,17]

Pharmaceutical Quality by Design (QbD) is a methodical, scientific, risk-based, all-encompassing, and proactive approach to pharmaceutical development that starts with established goals and emphasises product and process understanding and process control. It entails creating formulas and manufacturing procedures to meet predetermined product quality goals. In order to consistently produce a drug product with the desired characteristics, it is necessary to vary the critical process parameters. QbD identifies characteristics that are critical to quality from the perspective of patients, translates them into the attributes that the drug product should possess, and establishes how to do so. This requires establishing links between variables in the formulation and manufacturing processes and product qualities as well as identifying the causes of variability. The implementation of a flexible and reliable manufacturing process that can adjust and create a consistent product over time uses this knowledge.[18] Consequently, certain QbD consisting components are shown in figure.

The most crucial qualities drug products must possess to ensure their efficacy are frequently assessed by the assay and dissolution parameters. It is interesting to note that the QbD approach is currently used more often to determine assay limits than the QbT approach. With the exception of a few particular medications, where there are clinical justifications for smaller acceptance limits, such as 95-105%, the assay limit is often set to be 90-110%. It is uncommon to set assay limits using batch data. An assay limit of 90-110% would still be expected from a sponsor that regularly produced pharmaceutical products with an assay of 98–100%. Current dissolution acceptability limits, however, are chosen primarily on data from a small number of batches and their capacity to discriminate batches with little consideration for clinical relevance. The dissolution tests should be created in accordance with the QbD to reflect in vivo performance as closely as possible.[19] For instance, since dissolution is highly unlikely to be the rate-limiting step in vivo for BCS Classes I and III IR tablets, the acceptance criteria may be significantly broader than those from batch data (15,16). Similarly, in order to more accurately reflect in vivo dissolution, dissolution assays for BCS Classes II and IV medicines may need to be thoroughly investigated.[17] The impurity specification evaluates yet another crucial quality a medicine product must possess to guarantee its safety. Instead of using the actual batch data, the QbD requires that the acceptance threshold for an impurity be based on its qualification/biological safety level. Although toxicity studies may potentially be used to assess the biological safety level,[18] safety and/or clinical investigations are typically used to determine it. As a result, the standards for contaminants are typically found in clinical study materials or reference listed medications for generic medications.[18–20]

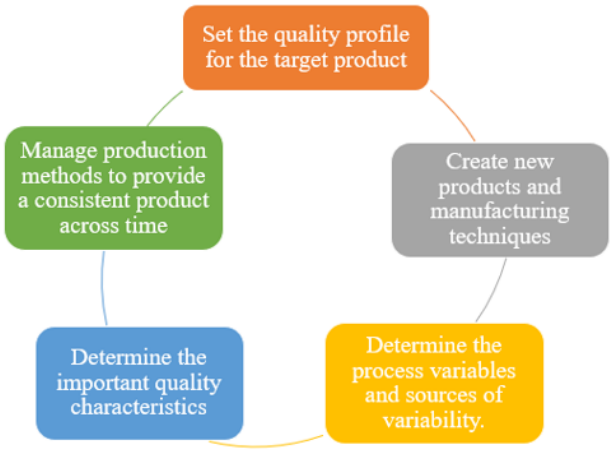

Figure 2: Components of QbD

10. Applications of Traditional Analytical Methods in QBD Process Development

The majority of QbD applications up to this point have not been analytical methods-focused, but rather have been implemented in the context of the overall pharmaceutical manufacturing process, with an emphasis on the process understanding gained through application of QbD principles, and in some cases, the development

of a design space and control strategy for a process.[19,20] Online process analytical technologies (PAT) are frequently used in the guise of QbD process development as analytical methodologies. When sufficient data is gathered, PAT may eventually lead to real-time release testing (RTRT) techniques, in which the need for end-product analytical testing to confirm product quality is eliminated because the real-time data gathered already offers a guarantee that the product is acceptable.[20,21] The ability of a process to purge chemical impurities is completely known through spiking experiments, and at-line and off-line analytical approaches have also been used in QbD impurity fate mapping (IFM) studies of genotoxic and nongenotoxic chemical impurities. Beyond individual analytical techniques and their outcomes, combinations of techniques are equally important for supplying input for more in-depth multivariate modelling of complex pharmaceutical processes, where various analytical measures are integrated to develop process understanding and attain control.[22] Multivariate techniques can be used to combine analytical measurements ranging from raw material chemical and physical attributes to intermediate granule density measurements to imaging analysis of end products to simulate the design space for a pharmaceutical process. Although the model is created for the process, the QbD control strategy as a whole is supported by the effectiveness of the analytical techniques and their findings.[23]

11. Conclusion

The primary goal of this study is to provide an overview of QbD and its characteristics in the contemporary pharmaceutical product development process. QbD focuses on reducing variability through continuous process improvement and integrating quality into the processes and products. The cost-effectiveness of QbD implementation is its most intriguing advantage. Being cost-effective means using the least amount of resources possible in the most efficient way, as QbD places an emphasis on constructing the required quality from the start of the cycle rather than spending money on failures and recalls. Being cost-effective does not mean a price drop from its peak value to value. The final step is the requirement for a collaborative effort of academia, industries, and regulatory agencies to start implementing QbD principles in practise. The necessary attributes for creating high-tech quality pharmaceuticals are established, gaps are recognised, and the next step is the necessity for these parties to work together. The purpose of this study was to establish communication within the pharmaceutical industry consortium regarding the application and use of PAT (such as online analysis and in situ analytics) in the sector. By demonstrating how, when, and why PAT is utilised, its value, and its significance to pharma, the authors aimed to provide typical and representative examples within the API process workflow that would increase awareness, inform and persuade suppliers, regulators, and pharma. The use of PAT tools for process control in a GMP manufacturing setting will be the subject of a later study. Critical parameters are identified and process parameter control limits are defined through process understanding. The number of process steps requiring real-time control can be reduced by the use of QbD principles, and the monitoring and control technology is to be made as simple as possible.

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None.

13. Conflict of Interest

None.

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