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QBD and PAT Tools in Drug Product Life Cycle

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ABSTRACT

In recent days quality, safety and efficacy of the products are the main focus, thus the regulatory bodies are emphasizing on implementing Quality by Design (QbD) and Process analytical tools (PAT), the science based approach for better products and process understanding by reducing process variation and enabling process-control strategies. The aim is to design a quality product and its manufacturing process to consistently deliver the intended performance of the product. Quality cannot be tested into products but quality should be built in by design. It includes the Quality target product profile (QTPP), critical quality attributes (CQA) and key aspects of Quality by Design. The foundation of Quality by Design is ICH Guidelines. Process analytical technology (PAT) has been defined as a mechanism to design, analyze and control pharmaceutical manufacturing processes through measurement of critical process parameters which affect critical quality attributes. The main goal of PAT is to provide successful tools such as multivariate data analysis and acquisition tools, modern process analyzers or analytical chemistry, endpoint process monitoring, controlling tools and continuous improvement and knowledge improvement tools. The objective of this article is therefore to provide a comprehensive understanding on various aspects of QbD and PAT in product life cycle, along with addressing the concerns related to its implementation to achieve the pharmaceutical process automation.

Keyword: Quality target product profile (QTPP), Critical Quality Attribute (CQA), Critical Process Parameter (CPP), Quality Risk Management (QRM), Process Analytical Technology (PAT).

I. INTRODUCTION

The Grapple of being human while tolerating from ill health, is happened on day by day from existing and will pursue as long as we alive throughout this process the healthcare workers and pharmacist are committee of professional group as old as human history have utilized different medicine from plant, animal and mineral for treatment of disease[1]. The expanding population of world causes alteration on welfare stages of society and living conditions. For this reasoning the health problems are increase. In this, condition, the human life quality is corresponding to the capability to produce the desired quality medicines. So, that the world pharmaceutical department is continuously upgrade and investigating in R&D and revolution is increase. In specific, the computer aided experimental design is anticipated to lower cost and increase quality in clinical research and production process. The FDA and European regulatory agency make definition of QbD as a systemic, scientific and risk-align approach to the manufacturing of pharmaceutical product from verifiable process. For Pharmaceutical dosage form the previous concept of Quality determination was by testing only, means from a batch of dosage form little random quantity of representative samples will be withdrawn for testing, results will determine the quality of the product. But the quality of each unit dosage is very crucial for the patient's perspective. Now the recent concept of Quality is 'Quality by Design', so that the quality is inbuilt by design from product inception stage onwards. It means the design of specifications of raw material, packaging material, finished goods and the formulation design, process design, process parameters design space etc., are to be considered or designed scientifically by using the relevant and effective scientific tools i.e., DOE to maintain quality by design throughout the product life cycle[2]. The conventional development process uses an empirical approach that requires continuous end product testing and inspection to determine quality. This approach ignores real-world variability in materials and process controls. At present, there is a different approach than yesterday. It's called Quality by Design (QbD). This is very scientific and logical. PAT is an integral part of QbD in the

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area of process control. In the absence of these two important elements i.e. QbD and PAT the pharmaceutical process automation is highly impossible in the product life cycle management. The QbD approach is now fully applicable for generic drug development, to achieve it. The regulatory authority always insists on implementing the ICH Q8 to Q10, in the relevant area of each part [3,4].

Quality by Design (QbD)[3-8]

For the pharmaceutical industry the plan, growth and manufacturing regulation of products and manufacturing procedure from the initial step to the final step of the product development phase for assuring the compatible quality of a pharmaceutical product. The QbD is a systematic scientific approach focused at meet the requirements of the patient in the desired and targeted quality and objective to produce the same quality standard product.

QbD is based is on the ICH Guidelines:

- ✓ Q8 for pharmaceutical development,
- ✓ Q9 for quality risk management,
- ✓ Q10 for pharmaceutical quality systems.

The objective of the pharmaceutical development is to design a quality product and its production process to consistently carry the desired product performance.

"Quality cannot be tested into products but quality should be built in by design."

A high quality drug product is a product free of contamination and reproducibly delivering the therapeutic benefit promised on the label to the consumer. ICH Q8 defines quality as "The suitability of either a drug substance or drug product for its intended use. This term includes such attributes as the identity, strength, and purity." A frequently used definition of quality is "Delighting the customer by fully meeting their needs and expectations". These may include performance, appearance, availability, delivery, reliability, maintainability, cost effectiveness and price, and total customer satisfaction. It is important that quality should be built in by design. To achieve the high level of quality there is need of Quality by Design.

Key characteristics of QbD

- ✓ A scientific tool for desired & efficient drug development.
- ✓ Vital and systematic process depends on the approach that quality can be built in as a continuum.
- ✓ It is applicable to drug product and excipient.
- ✓ Substance development (chemicals /biologics).
- ✓ It is applicable to analytical methods
- ✓ It can be apply partially or totally
- ✓ It can be used at any time in the life cycle of the drug
- ✓ Always boost by regulators

ICH Q8: Pharmaceutical Development

It discusses the numerous components of quality by design. These in combination with the form the Fundamental basis for the QbD approach to development.

It involves the following key elements during pharmaceutical development-

1. Define the quality target product profile
2. Identify the quality attributes
3. Perform a risk (assessment) analysis
4. Determine the critical quality attributes and critical process parameters
5. Determine the design space
6. Identify a control strategy

Steps involved in quality by design products:-

1. Development of new molecular entity

- ✓ Preclinical study
- ✓ Nonclinical study
- ✓ Clinical study
- ✓ Scale up
- ✓ Submission for market approval

2. Manufacturing

- ✓ Design space
- ✓ Process analytical technology
- ✓ Real time quality control

3. Control strategy

- ✓ Risk based decision
- ✓ Continuous improvement
- ✓ Product performance

Quality by design (QbD) and well understood product and processes.

- ✓ All expository sources of irregularity are identified and explained.
- ✓ Variability is managed by the process.
- ✓ Product quality assign can be accurately and dependability predicted over the design space established for materials used, process parameters, environmental and other condition.
- ✓ To obtain enhanced knowledge of product performance over a range of material

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attributes, production process options and process parameters considering.
- ✓ Proper use of quality risk management fundamentals.

Systemic approach to development:
- ✓ That begins with predefined objectives
- ✓ Emphasizes products and process understanding
- ✓ Process control

The following are the very important elements of QbD:
- ✓ Quality Target Product Profile (QTPP)- The product design
- ✓ Critical Process Parameter (CPP)
- ✓ Critical Quality Attributes (CQA)
- ✓ Critical Material Attribute (CMA)
- ✓ Design Space (DS)
- ✓ Design of Experiments (DOE)
- ✓ Control strategy
- ✓ Quality Risk Management (QRM)
- ✓ Operating Space or Range
- ✓ Process Validation

CERTAIN KEY ASPECTS OF QBD

The Target Product Quality Profile

Target Product Quality profile (TPQP) is a tool for setting the strategic foundation for drug development "Planning with the end in mind."

Drug substance and excipient properties

To regularly achieve the drug-product quality stated in the label, the drug substance necessary to be thoroughly characterized with respect to its physical, chemical, biological and mechanical properties such as solubility, polymorphism, stability, particle size, and flow properties.

Production process design and development

The first stage of process development, in which summery of the commercial manufacturing processes is reported, including the intended scale of manufacturing. The factors that need to be contemplate for the arrangement of the process, counting facility, equipment, material transfer, and manufacturing variables. Other factors to consider during process development are the QTPP and CQAs.

Product quality by end product testing vs QbD

Comparison between product qualities by end product testing vs. quality by design-

Designed to consistently meet desired product quality-
- ✓ Design space idea
- ✓ Tentatively defined process running space depends on methodical principles.
- ✓ Critical process parameters recognized.
- ✓ Critical influence product quality

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- ✓ Space operating range yielding acceptable product space.
- ✓ Critical process parameters are consistently managed.
- ✓ Product of process is always desired quality product.
- ✓ End product testing might be reduced.

Designed to facilitate continuous improvement

- ✓ Process regulates strategy
- ✓ Execution and continual process development.
- ✓ Real time process response process improvement within design space knowledge builds with experience attachment information/new technologies to improve process efficiency key opportunity to continuously improve the process.

E.g. Increased supply, more competence.

Applications of Quality by Design (QbD) [9]

Quality by design (QbD) – a comprehensive systematic approach to pharmaceutical development and manufacturing advancement in the pharmaceutical development and manufacturing by QbD can be explained against traditional approach.

In pharmaceutical development

- ✓ To design a quality product and a manufacturing process to consistently deliver the intended performance of the product.
- ✓ In life cycle management
- ✓ Continual improvement enabled within design space.

QbD in CMC Review Offices

- ✓ Office of New Drug Quality Assessment (ONDQA)
- ✓ Science-based assessment
- ✓ Restructured organization and reorganized staff –
- ✓ premarket staff and post market
- ✓ CMC Pilot
- ✓ A number of applications submitted
- ✓ Lessons learned
- ✓ Evaluation of information
- ✓ Implementation of PMP

Office of Generic Drugs (OGD)

- ✓ QbD contains the important scientific and regulatory review questions.
- ✓ Evaluate whether a product is of high quality.
- ✓ Determine the level of risk associated with the manufacture and design of this product.
- ✓ 416 applications received using QbD by June 2007.
- ✓ Successful in ensuring that questions address issues regarding QbD.

Benefits of implementing QbD for FDA

- ✓ Enhances scientific foundation for review,
- ✓ Provides for better coordination across review,
- ✓ Compliance and inspection,
- ✓ Improves information in regulatory submissions,
- ✓ Provides for better consistency,
- ✓ Improves quality of review (establishing a QMS for CMC),
- ✓ Provides for more flexibility in decision making,
- ✓ Ensures decisions made on science and not on empirical information,
- ✓ Involves various disciplines in decision making,
- ✓ Uses resources to address higher risks.

Benefits to Industry

- ✓ Ensures better design of products with less problems in manufacturing,
- ✓ Reduces number of manufacturing supplements required for post market changes –rely on process and risk understanding and risk mitigation,
- ✓ Allows for implementation of new technology to improve manufacturing without regulatory examination,
- ✓ Allows for possible reduction in overall costs of manufacturing –less waste,
- ✓ Ensures less hassle during review –reduced deficiencies –quicker approvals,
- ✓ Allows for continuous improvements in products and manufacturing process.

Quality risk management

- ✓ The FDA defines a Risk Management as, a strategic safety program designed to decrease product risk by using one or more interventions or tools.
- ✓ It is systematic process for the assessment, control, communication and review of risks to the quality of the drug product across the product life cycle.
- ✓ The ICH Q9 guideline: Quality Risk Management provides a structure to initiate and follow a risk management process.

Advantages of QbD-

There are many advantages of QbD as enlisted below:

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- ✓ It minimizes or eliminates the potential compliance actions.
- ✓ It provides opportunities for continual improvement.
- ✓ It facilitates innovation.
- ✓ It enhances opportunities for first cycle approval.
- ✓ It is cost saving and efficient for the industry.
- ✓ It increases process capability and reduce product variability and defects.
- ✓ It eliminates batch failures.
- ✓ It empowers technical staff.
- ✓ It provides better understanding of the process.
- ✓ It ensures better design of product with fewer problems.

Overview of a typical quality risk management process is given in figure below.

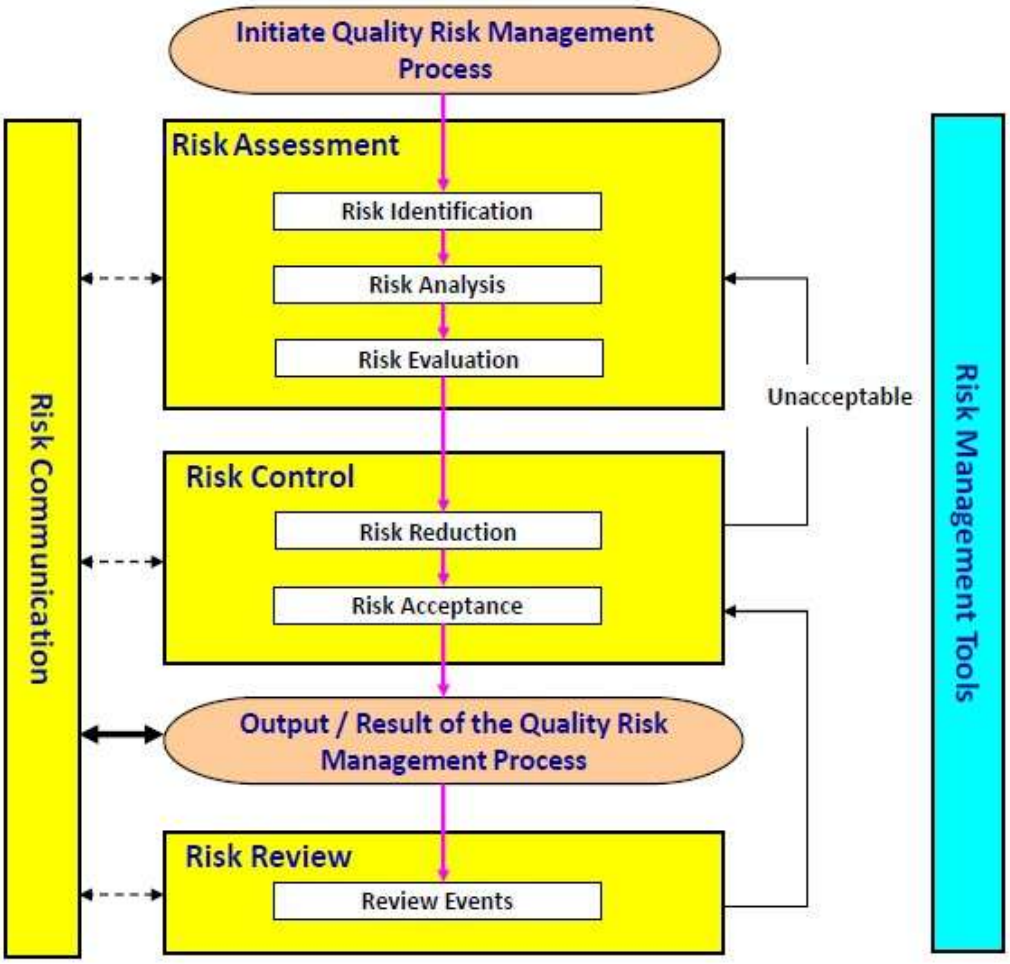

Figure 1: Typical Quality risk management process

Failure mode effects analysis (FMEA)

FMEA is one of the most commonly used risk-assessment tools in the pharmaceutical industry. It is a systematic and proactive method to identify and mitigate the possible failure in the process. Failure modes represent any errors or defects in a process, material, design, or equipment. Once failure modes are established, FMEA tool evaluates the effect of these failures and prioritizes them accordingly. This tool is further advanced with studying criticality of the consequences and providing clear indication of the situation.

Failure Mode, Effects and Criticality Analysis (FMECA)

It is the extension of earlier said FMEA tool. Extending FEMA to incorporate an investigation of the degree of severity of consequences, their probabilities of occurrence and their detect-ability is Failure mode, effects and criticality analysis. In FMECA, each failure mode

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of the product is identified and then evaluated for criticality. This criticality is then translated into a risk, and if this level of risk is not acceptable, corrective action must be taken. This can be utilized for failure and risk associated with manufacturing processes. The tool can also be used to establish and optimize maintenance plans for repairable systems and contribute to control plans and other quality assurance procedures.

Fault tree analysis (FTA)

This tool assumes failure of the functionality of a product or process. The results are represented in the form of a tree of fault modes. This can be used to investigate complaints or deviation in order to fully understand their root cause and ensure that intended improvement will resolve the issues and not cause any other different problem.

Process Analytical Technology (PAT) [10-13]

It is part of a design quality approach that is used to design, analyze, and control real time measurements of quality and performance criteria for raw and processed materials to achieve the desired final product.

This scientific and systematic approach to pharmaceutical product development, which is also acknowledged and supported by the health authorities, serves to the changing and developing pharmaceutical sector.

Process Analytical Technology steps-

PAT consists of three main steps is the form of the interrelated design, analysis and control.

- ✓ In determining the quality of the final product at the design step, it is necessary to determine the level of effects of each process step and starting material.
- ✓ In the analysis step, direct or indirect analytical tools are used in real time to determine the quality features of the process materials and raw material.
- ✓ In the last step, the harmony between all the results obtained through a process control is evaluated.

PAT is used in different fields of the pharmaceutical industry such as extraction and crystallization processes, production of solid dosage forms, tablet pressing, quantification of active and auxiliary substances, blending, granulation, and coating processes. Improving understanding of multiparticulate drug delivery system by monitoring percent weight build up during the functional coating process of drug loaded pellets within QbD framework.

For this purpose, Fourier Transform Infrared and Raman spectroscopy instruments were used as PAT tools.

Table 1: PAT Application in Pharmaceutical Process

Unit Operation	PAT Tools (Online)
Raw material identification	Near Infrared (NIR), Raman
High shear wet granulation process	Torque meter, NIR, PARSUM, Acoustic Emission, FBRM
Low shear wet granulation process	NIR, PARSUM, FBRM
Reaction Monitoring	NIR
Crystallization	FBRM
Fluidized Bed Drying	NIR
Mixing, Blending and Lubrication	NIR
Tablet Compression	NIR
Coating	Droplet Size measurement, NIR

How PAT works – an instant

The first step away from off-line testing would be at-line testing. This is the movement of process dedicated testing equipment to the production line to provide rapid results. One advantage is the elimination of transfer of samples involving time delays. Apart from traditional tests such as dissolution, assay, friability, hardness and thickness this could also include accelerated dissolution rate analysis, and near infrared tablet analysis.

PAT in development

- ✓ PAT is usually linked with in-process quality control testing in commercial manufacturing. However, in order to successfully implement PAT, sufficient knowledge of the

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process/product has to be gained in the early stages of development.

- ✓ As part of QbD effort, PAT opportunities can be identified in early development. However, since the success rates for compounds in early development are low, it is recommended that PAT application be initiated in the later phase of development.

PAT in commercial manufacturing

- ✓ When designing a control strategy, a useful technique is to focus on the first three PAT tools and to apply them individually to evaluate each manufacturing step. Process controls, (the third tool in the PAT system) are an integral part of the control strategy and are designed based on process knowledge (gained from multivariate tools) and process information (gained from analyzers).
- ✓ There are different levels of process control. One level is the proper design and construction of manufacturing equipment so that it is suitable for its intended purpose and can achieve the required quality.
- ✓ These tools (multivariate design/analysis, and process controls), should be applied together with process analyzers as a system. The advantage of considering each tool separately when creating the system is that it facilitates good decision making.
- ✓ The fourth PAT tool, continuous improvement and knowledge management, is also linked with the other three but it can appear later in the design of a control strategy. It becomes extremely important in the life cycle of manufacturing quality assurance systems.
- ✓ Continuous improvement also means that constant evaluation of potential quality assurance improvement opportunities should be made. It may be appropriate to conclude that, if the quality assurance system includes some amount of finished product testing, then opportunities are available to improve upon the PAT tools that are in place.

PAT regulatory approach

- ✓ PAT can be implemented under cGMP Implementation by PAT team or PAT certified investigator.
- ✓ A supplement can be submitted to the agency
- ✓ A protocol can be submitted to the agency
- ✓ After approval of protocol by agency then manufacturer may request to a FDA PAT team for inspection of preoperational review of a PAT implementation

PAT regulatory guidance

- ✓ Regulatory agencies like US-FDA ICH, ASTM etc. who has been active in the area of PAT in the development of standard for use of PAT in pharmaceutical industry internationally in their standards committee E55.
- ✓ US-FDA was published PAT final guidance in SEP 2004.

How PAT works?

- ✓ Selection of process
- ✓ Selection of suitable PAT system
- ✓ Identification of CPP (critical process)
- ✓ Design process –
- ✓ 1) On line test 2) In line test

Types of PAT implementation-

- ✓ Initial phase – process optimization
- ✓ Scale -up phase – Comparing data
- ✓ Temporary process – gaining process info and understanding process
- ✓ Permanent process – actual process monitoring and control.

PAT Analysis is better than Lab. Analysis because-

- ✓ Control environment
- ✓ Speed
- ✓ Operator error
- ✓ Safety
- ✓ Sample integrity

Advantages

- ✓ Reduction in production cycle time
- ✓ Preventing reprocessing and rejecting
- ✓ Increase automation
- ✓ Improve operator safety
- ✓ Reduce human error
- ✓ Improving energy and material use and increase capacity
- ✓ Continuous process
- ✓ Controlling variability
- ✓ Continuous improvement and knowledge management

Disadvantages

- ✓ Require efforts during design
- ✓ Implementation and management stages is high
- ✓ Require specialized, expertise person
- ✓ Costly

PAT tools

There are many current and new tools available that enables scientific, risk management pharmaceutical development, manufacture, and

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

Multivariate data acquisition and analysis tools-

From a physical, chemical, or biological perspective, pharmaceutical products and processes and processes are complex multi-factorial systems. There are many different development strategies that can be used to identify optimal formulation and process conditions for these systems. The knowledge acquired in these development strategies that can be used to identify optimal formulation and process condition for those systems. The knowledge acquired in these development programs are the foundation for product and process design. Experiments conducted during product and process development can serve as building blocks of knowledge to grow to accommodate to a higher degree of complexity throughout the life-cycle of a product. Information from such structured experiments supports the development of a knowledge system for a particular product and its processes. These experimental databases can also support the development of process simulation models, which can contribute to continuous learning and help to reduce overall development time.

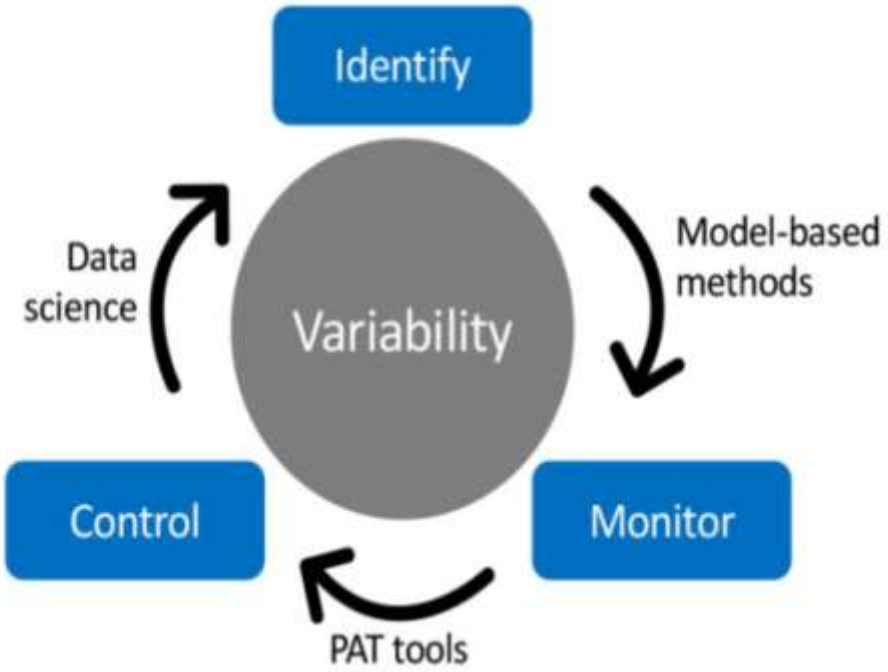

Figure 2: PAT tools

Modern process analyzers or process analytical chemistry tools

Process analytical chemistry as a discipline has grown significantly during the past several decades, due to an increasing appreciation for the value of collecting process data during production. From the simple process measurement such as pH, temperature and pressure, modern tool that measure chemical composition and physical attributes have evolved.

These modern process analysis tools provide non-destructive measurements that contain information related to both physical and chemical attributes of tae material being processed. These measurements can be performed in the following manner:

- ✓ Offline in a laboratory
- ✓ At line in the production area, during production close to the manufacturing process

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- ✓ Online where measurement system is connected to the process via a diverted sample stream; the sample may be returned to the process stream after measurement
- ✓ In line where process stream may be disturbed (e. g. probe insertion), and measurement done in real time
- ✓ Non-invasive, when the sensor is not in contact with the material (e. g., Raman spectroscopy through a window)in the processor, the process stream is not disturbed

Process and endpoint monitoring and control tools

Following steps can be included for design and optimization of drug formulations and manufacturing process within the PAT framework:

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 relationship between product quality attributes and
5. Measurement of critical material and process attributes.
6. Therefore, it is important to emphasize that a strong link between product design and process development is essential to ensure effective control of all critical quality attributes. Process monitoring and control strategies framework, a process endpoint need not be a fixed time, but can be the achievement of the desired material attribute. This, however, does not mean that process time is not considered. A range of acceptable process times (process window) is likely to be achieved during the manufacturing phase and should be evaluated; considerations for addressing significant deviations from acceptable process time should be developed. Process end points intended for use in real-time release should be considered more critical than those that are only used for in process control.
7. Continuous improvement and knowledge management tools
8. Continuous learning through data collection and analysis over the life cycle of a product is important. Data can contribute to justifying a proposal for post-approval changes including the introduction of new technologies. Approaches and information technology system that support knowledge acquisition from such databases are valuable for the manufacturers and can also facilitate scientific communication with the regulatory agency.
9. Strategy for implementation
10. The Agency understands that to enable successful implementation of PAT, flexibility, coordination, and communication with manufacturers is critical.

The Agency believes that current regulations are sufficiently broad to accommodate these strategies.

The Agency's regulatory strategy includes the following:

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

II. CONCLUSION

The basic principle of QbD is that quality should be built into a product with an understanding of the product and process by which it is developed and manufactured along with a knowledge of the risks involved in manufacturing the product and how best to mitigate those risks. QbD has major advantages in the development of a pharmaceutical company. It is a systematic, scientific and risk-based approach to the development of every step that is involved in the manufacturing. PAT Tools also has major applications in the development. PAT designs, analyses and controls the quality assurance of the drug, which is the product of the industry. PAT along with QbD is used for designing, constructing and controlling the quality of the product. QbD is also called the “best practice” for pharmaceutical product development. An important aspect of QbD is under standing and controlling the manufacturing process for the product.

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