



Review Article

The Colossal Role of QbD and PAT Tools in the Pharmaceutical Process Automation

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ARTICLE INFO

A B S T R A C T

Received: 12 Dec 2017

Accepted: 28 Dec 2017

Pharmaceutical industry has been always emphasizing on product quality, efficacy and safety. Now a day's the process automation also being considered which heading Pharmaceutical Industry. The traditional quality by testing (QbT) approach was being followed in older days. The product quality and performance are predominantly ensured by end product testing, with limited knowledge of the product, process and critical process parameters. Recently these quality, safety & efficacy of the products are the prime requirements, thus the Regulatory bodies are focusing on implementing quality by design (QbD) and Process analytical tools (PAT), which are the science based approach for better products and process understanding by reducing process variation and the enabling process-control strategies. In this regards, pharmaceutical industry is currently undergoing a significant transformation to streamline their Research and Development (R&D) process, provide greater manufacturing flexibility and control, and to reduce regulatory burden. However, till date there is limited understanding and major concerns regarding the implementation of QbD principles and PAT in the pharmaceutical arena. The objective of this article is therefore to provide a comprehensive understanding on various aspects of QbD and PAT, along with addressing the concerns related to its implementation to achieve the automation in the pharmaceutical process.

KEYWORDS: Quality by design, PAT, Design of experiment, Pharmaceutical manufacturing, Critical quality attributes, Quality risk management and Design space.

1. INTRODUCTION

In earlier days, the concept for quality determination of Pharmaceutical dosage form was based on testing only. From a batch of dosage form, little random quantity of samples will be withdrawn for testing; results will be determine and the quality of the product shall be mentioned. But the quality of each unit dosage is very important in respect to the end user's desired purpose. So Now the recent

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concept of Quality is ‘Quality by design’, So that the quality is inbuilt by design. It means the design of Specifications of raw material, packing material, finished goods and the formulation design, process design, process parameters design space, are to be considered or designed scientifically by using the relevant and effective scientific tools to maintain quality by design throughout the product life cycle^{1,2}. 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 path. It’s called Quality by Design (QbD). With QbD approach we can get a proactive approach to product development, will give sufficient knowledge and understanding of the process, critical process parameters and control strategy in turn reduces the Food Drug Administration (FDA) queries. QbD also review time on submitted dossier, and in the product life cycle management in case of any deviation or failure. All these scientific data help to identify the root cause, risk mitigation plan and resolution. The knowledge obtained during development helps to justify the establishment of a design space, (process) control strategy and set point within the (regulatory approved) design space. To give a full shape to QbD, the PAT is very important part. PAT is an integral part of the QbD in the area of Process Control. In Absence of these two important elements i.e. QbD and PAT, the pharmaceutical process automation is highly impossible. The QbD approach is now fully applicable for the generic drug Development, to achieve it. The regulatory authority always insists to implement the ICH Q 8 to Q11, in the relevant area of each part^{3,4}. To address the subject article we need to understand thoroughly both QbD and PAT.

What Is Quality By Design?

As per ICH Q8, the Quality by Design (QbD) is a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. The Quality by Design (QbD) is a advanced, scientific approach that develop product design, automates manual testing, and streamlines troubleshooting. It uses a systematic approach to ensure quality by developing a thorough understanding of the compatibility of a finished product to all of the components and processes involved in manufacturing that product. Instead of relying on finished product testing alone, QbD provides insights upstream throughout the development process. As a result, a quality issue can be efficiently analyzed and its root cause quickly identified. QbD requires identification of all critical formulation attributes and process parameters as well as determining the extent to which any variation can impact the quality of the finished product. The more information generated on the impact – or lacks of impact – of a component or process on a product’s quality, safety or efficacy, the more business flexibility

Quality by Design provides. The QbD has various components like quality target product profile (QTPP), critical quality attributes (CQA), critical process parameter (CPP), critical materials attributes (CMA), Design Space, design of experiment (DOE), Control Strategy with quality risk management (QRM), Operating Range and Process Validation⁵⁻⁷.

Quality Target Product Profile (QTPP) – The product Design:

The QTPP identifies all the critical quality attributes (CQA) for the product. QTPP is a prospective summary of the quality characteristics of a drug product that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the drug product. The QTPP includes the factors that define the desired product and the CQAs include the product characteristics that have the most impact on the product quality. These provide the framework for the product design and understanding. The components are characterized and the compatibility of the components is evaluated. The quality target product profile forms the basis of design for the development of the product. Considerations for the quality target product profile could includes, intended use in clinical setting, route of administration, dosage form, delivery systems; dosage strength(s); container closure system; therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g., dissolution, aerodynamic performance) appropriate to the drug product dosage form being developed; drug product quality criteria (e.g., sterility, purity, stability and drug release) appropriate for the intended marketed product⁸.

Critical Quality Attributes:

A CQA is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQAs are generally associated with the drug substance, excipients, intermediates (in-process materials) and drug product. CQAs of solid oral dosage forms are typically those aspects affecting product purity, strength, drug release and stability. CQAs for other delivery systems can additionally include more product specific aspects, such as aerodynamic properties for inhaled products, sterility for parenterals, and adhesion properties for transdermal patches. For drug substances, raw materials and intermediates, the CQAs can additionally include those properties (e.g., particle size distribution, bulk density) that affect drug product CQAs. Potential drug product CQAs derived from the quality target product profile and/or prior knowledge is used to guide the product and process development. The list of potential CQAs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. Quality risk management can be used to prioritize the list of potential CQAs for subsequent evaluation. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that

assesses the extent to which their variation can have an impact on the quality of the drug product⁹⁻¹⁰.

Critical Process Parameter (CPP):

A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality. CPP will be identified during the product and process development with the help of DOE¹¹.

Critical Material Attribute (CMA):

A physical, chemical, biological or microbiological property or characteristic of an input material that should be within an appropriate limit, range, or distribution to ensure the desired quality of output material¹¹.

Design Space:

It is defined as the multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. Understanding of processes is the key to defining the design space. Critical process parameters (CPPs) are identified by determining the extent to which any process variation can affect the quality of the product. When design space is known then it is easy to anticipate issues and plan how to control the process. Actual experimental data, product experience, or literature guidance can be used to define the extremes of the parameter sets to be refined¹².

Design of experiments (DOE):

It is a systematic method to determine the relationship between factors affecting a process and the output of that process. In other words, it is used to find cause-and-effect relationships. This information is needed to manage process inputs in order to optimize the output¹².

Control strategy with Quality Risk Management (QRM):

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications, and the associated methods and frequency of monitoring and control (ICH Q10). Based on the process design space, a well-executed control strategy can be defined. This enables to understand the processes in a way that ensures product quality from known variability of the production process. This disciplined approach will keep the complex production processes under control. One technique to help avoid such a disparity is to conduct a Design of Experiments (DOE) study on the product in the development stage. Considerable wasted effort can be eliminated with such an approach as can any unexpected adverse outcome from the lack of control strategy understanding during the

product life cycle management. We need to understand QRM and its different relevant components^{12,13}.

Quality risk management (QRM):

It is a systematic process for the identification, assessment, control, communication and review of risks to the quality of the drug product across the product lifecycle. Quality Risk Management within the Pharmaceutical Industry. Every product or process has associated risks. Zero risk reduction is not a realistic goal nevertheless protection of patient by managing this risk in the quality system and manufacturing process is being given prime importance in the pharmaceutical industry. FMEA - Failure modes and effects analysis (FMEA) is a step-by-step approach for identifying all possible failures in a design, a manufacturing or assembly process, or a product or service. "Failure modes" means the ways, or modes, in which something might fail. FMEA is used during design to prevent failures¹²⁻¹⁴.

Operating Space or Range:

The operating space is the best set of parameters, determined statistically with the help of DOE, which enable to accommodate any natural variability due to input material or process input in CPPs and CQAs. For generic products, the operating space should be within the control space (which was defined during product development with the help of statistical tool like DOE) and should allow a reference product to be tested with the same set of parameters. For new products, the operating space of range should be within the design space and compliant with regulatory guidelines. Innovators can gain a competitive advantage by thoroughly exploring the design space, including testing multiple batches of formulations to truly refine their product¹⁵.

Process Validation:

The process validation is defined as the collection and evaluation of data, from the process design stage through commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality product. Process validation involves a series of activities taking place over the lifecycle of the product and process. This guidance describes process validation activities in three stages. Stage 1 – Process Design: The commercial manufacturing process is defined during this stage based on knowledge gained through development and scale-up activities. Stage 2 – Process Qualification: During this stage, the process design is evaluated to determine if the process is capable of reproducible commercial manufacturing. Stage 3 – Continued Process Verification: Ongoing assurance is gained during routine production that the process remains in a state of control during the product life cycle^{16,17}.

2. THE BENEFITS OF QbD

Proper implementation of QbD can potentially provide three main benefits for development that are more efficient use of development time and costs, ability to meet FDA submission

guidelines and expectations and reduced approval times and fewer queries from the FDA¹⁷.

Likewise, QbD can potentially provide significant benefit in manufacturing. Even after the drug has gained FDA approval, during product life cycle in routine QC testing may detect an out of specification (OOS) result. However it is very easy to address the OOS & have effective CAPA in presence of sufficient QbD data. But for a company that did not use a QbD approach, an OOS result can mean a seemingly endless quest to find the root cause. Absent the data that QbD provides, test results may be suspected, the questions difficult to answer, and long delays inevitable. Without knowing where to look, the team may resort to a trial-and-error approach to resolve any OOS occurrences¹⁸.

Even that could cause a 4- to 9-fold increase in testing to clear up an OOS investigation – a costly affair and time-consuming prospect in commercial scale. The impact of poor quality development work that spirals out of control into an OOS event during product life cycle can be horrendous¹⁸.

For manufacturers, there are potentially huge external costs for delayed product launches or approvals, or severe actions such as consent decrees, the internal costs of wasted raw materials, scrap batches, and the cost of investigation and remediation⁹. Importantly the damage to the brand such an event would have. To add further insult, the company may have to spend an enormous amount of money just to get your product back to market, and overall business loss and reputation at stake¹⁸.

QbD minimizes these risks by mapping all the possible variables of the product attributes and processes into a known control space. This means that if any quality issues occur, the scientific team can use specific methods to quickly pinpoint the scientific variables that are most likely causing the issues¹⁹.

The business benefits can be significant, including; fewer lost batches, resulting into revenue, market share & Business loss. Fewer manufacturing deviations, saving hundreds of costly hours. Faster time to market and more reliable supply, when each day on the market could generate the revenue. Fewer inspections of manufacturing sites. A many-fold ROI via cost savings and increased revenue¹⁹.

3. THE CHALLENGES OF ADOPTING QbD

Despite the many financial and operational benefits of QbD, and even with the new FDA recommendations, not all companies have adopted this approach. As the saying goes “you either pay now, or pay later.” Implementing QbD beginning at the development phase requires a dedicated, disciplined, and sustained commitment by an organization. Understanding the effort necessary to implement QbD is a key component to successful adoption. Some of the most common barriers to adoption include: Insufficient understanding of the process and its benefits, Organizational resistance to change, Denial of the need (Our process is

under control), Competing priorities and Lack of resources and expertise in QbD²⁰.

When you consider the tremendous potential financial gain, faster time to market, process improvements, and quality assurance generated by a successful implementation of QbD, these obstacles seem to pale in comparison²⁰.

The FDA expects at least these QbD components in all submissions: that are Quality target product profile (QTPP), list of critical quality attributes (CQAs), list of critical material attributes of drug and excipients (CMAs), list of critical process parameters (CPPs) and a control strategy that ensures the product reliability meets its predefined objectives.

The FDA clearly sees QbD as the way to enhance the quality of drug products for the benefit of everyone involved: Manufacturers will save time and money developing and producing drugs. Regulators will save time and resources approving drug applications, conducting inspections, and troubleshooting quality issues. Patients will be assured of more consistent, high-quality drug products that always meet safety and efficacy requirements. In the eyes of the FDA and the many advocates of QbD, the approach represents a way to “do more with less” and gain a winning outcome for manufacturers, regulators, and patients. Proper implementation of QbD can potentially provide several benefits for development and manufacturing: more efficient use of development time and costs, ability to meet FDA submission guidelines and expectations, reduced approval times – and fewer queries –from the FDA and rapid response to any manufacturing deviation.

The impact of poor development that spirals out of control for the marketed product can be devastating. Fortunately, these costs and delays can be avoided by using QbD, a more modern, scientific approach that formalizes product design and development and eliminates troubleshooting by trial-and-error. Despite the numerous tangible benefits of QbD, most companies do not understand the concept, appreciate its value, or know how to implement it effectively. Successful implementation of QbD requires a dedicated, disciplined, sustained commitment. Additionally, a sense of urgency now exists as the FDA began strongly encouraging all drug product applicants to use QbD. Deficiency letters will now explicitly cite the lack of QbD. QbD is a scientific method to define product and process design during the development stage to produce consistent quality during product life cycle, however in the product life cycle to monitor and control the critical and key process parameters in turn quality of drug product, the role of PAT tools is very important. So it is very obvious to establish the relationship between QbD and PAT tools, especially when we are depending on process automation for quality, safety and efficacy of the product^{20,21}.

What is PAT?

It is an Advance tool for designing, analyzing and controlling Pharmaceutical Manufacturing Process through

timely measurements (i.e. on line, off line, in line) of Critical Quality and performance attributes for raw and in process Materials & processes with the objective of ensuring the product desired quality. Concept of PAT is based on identification and control of risks during the manufacturing of drug product¹⁴.

Importance of PAT:

It effectively builds quality into products; also eliminate the process variation resultant into process safety. It also helps to understand the manufacturing process and its control in totality²¹.

Different levels of PAT Implementation:

Preliminary stage is Capturing of Manufacturing Process Parameters. Scale up stage is Evaluation of process parameters Data. Provisional Stage is Process Understanding. Permanent Stage is Actual process Monitoring and Process control by Implementing PAT Tools²¹.

PAT Analysis is preferred over conventional Laboratory Analysis:

Followings are the reason, why PAT is preferred that are Faster or online results are available, which helps to take the decision to release the batches for the consumption, PAT eliminate the Human error, It is safe to product, Human and Environment, It increases the productivity and During analysis sample integrity exists^{20,21}.

The online PAT tools are having capability to monitor & control the process as per defined parameters; hence such online PAT tools are very helpful for the Process Automation. Therefore if such online PAT tools are employed in the process to monitor the process we can ensure the process control without human interference, which is eventually termed as process automation. For example process are defined as per design space, in the running process due to influence of any factor if the process parameters are deviated from the defined process and if process equipment are looped through the PAT tools then in that case because of vigilance and backward intimation capability of PAT tools to the HMI/PLC, the process parameters will be always within the range of Design Space²².

For instance let us assume the Pelletization process in Wurster coater, where the bed moisture is very critical requirement for the Pelletization process. At particular bed moisture content only the process will run smooth, or else there will be an occurrence like agglomeration or static charge generation. In this particular case the NIR can be employed as one of the effective PAT tools, where NIR will measure the pellet bed moisture online and will inter link with control measure for the moisture like Inlet temperature, Inlet air flow, Spray rate etc as electronic backward intimation and control the desired the bed moisture content. Thus the PAT tools play a very critical role in process automation²².

PAT Tools – Off line:

Powder Flow Meter parameter is used to characterize the Powder physical properties like Flow Rate and Angle of repose. Powder Rheometer parameter is used to characterize the Powder physical Properties and measures the Energy and force like Basic flow energy, Aeration Energy, Permeability Energy, Compressibility, Shear Cell force, Wall friction force and Stability energy²².

PAT includes other benefits as it enhances the productivity, it exterminates the human intervention as a result upturn the automation, it ensures the operator's safety, it corrects on line the process variation so resultant into elimination of the variability in the process and it creates the data bank and in turn guides for continuous improvement plan²².

4. CONCLUSION

QbD design the process and the process parameters, however PAT has the capability to monitor and control the process. So to make an error free robust process, the joint role of both QbD and PAT is very significant. Both the QbD and PAT are very imperative to each other in the process. That is how the QbD and PAT both are playing very significant role in the Pharmaceutical process automation.

5. ACKNOWLEDGEMENT

Authors wish to thanks Oman Pharmaceuticals, Jeypore College of Pharmacy and Institute of Pharmacy & Technology for proving information through library facility to carry out literature study.

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Conflict of Interest: None

Source of Funding: Nil