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A QUANTITATIVE APPROACH FOR PHARMACEUTICAL QUALITY BY DESIGN PATTERNS

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Abstract

Pharmaceutical industry is moving towards quality. Many pharmaceutical companies have used several Quality Management System (QMS) for instance ISO 9001. Design process has one of the most important factors that contributing in pharmaceutical product quality. The pharmaceutical industry is used the concept of Quality by Design (QbD) to apply science-based manufacturing principles for new and existing products to assure quality of the formulation. In a first step, the QbD-methodology is systematically used to establish the critical quality attribute identify potentially critical input factor and these factors to define activities for process characterization. A process DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs, and establish design space to ensure desired CQAs. Critical material and process parameters are linked to the critical quality attributes of the product. Experiments were designed with focus on critical material and process attributes. Quality by design is an essential part of the modern approach to pharmaceutical quality. The purpose of this article is to discuss the use of Quality by Design (QbD) in pharmaceuticals and describe how it can be used to ensure pharmaceutical quality. Process parameters and quality attributes were identified for each unit operation. The design space was established by the combined use of DOE, optimization and multivariate analysis to ensure desired CQAs. Multivariate analysis of all variables from the DOE batches was conducted to study relationships between the variables and to evaluate the impact of material attributes/process parameters on manufacturability and final product CQAs.

Keywords: Quality by design, Critical quality attributes, Design space, Quality Management System.

Introduction

Quality is one of the most critical performance measures that can significantly affect a manufacturer's competitiveness. One is related to the quality of the product design, which requires designing the product. The other factor is the degree of approval of the manufactured products to the design specifications. In the manufacturing system design on quality at the early stages of system development helps achieve high-quality products at lower costs. Several methods and approaches are reported for assessing and predicting quality. Now days, statistical quality control methods have been extensively used to assess quality performance and capabilities of the manufacturing processes.

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QbR is a recent approach in quality assessment system that is focused on critical pharmaceutical quality attributes. The main benefits of this QbR system are to assure product quality through design and performance based specifications facilitate continuous improvement. The concept of QbD was mentioned in the ICH Q8 guidance which states that "quality cannot be tested into products, i.e., quality should be built in by design". In this article shows the pharmaceutical quality by design and describes how it can be used to ensure pharmaceutical quality with emphasis on production of solid or liquid dosage form in pharmaceutical companies. The pharmaceutical industry works hard to develop, manufacture, and bring to market new drug and to comply with regulatory requirements to assure that the drugs are safe and effective. A new approach to drug development could increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits throughout the product's life cycle.

Software quality has been a modern approach since the early days of pharmaceutical engineering. Recently, a number of practitioners have shown great interest in using design patterns for high-quality software. The development of software becomes an expertise of the machines, and human interaction is necessary for approving the designs and finished products. The design phase is dictates the quality levels that could be achieved pharmaceutical products and processes. Scientific understanding of the relevant multi-factorial design usually requires the use of multivariate approaches, such as statistical design of experiments, response surface methodology, optimization and multivariate data in conjunction. The QbD approach began with a predefined target product profile (TPP), and applies various principles and tools at different stages to better understand the product. Quality risk assessment (QRA) tools, such as risk filtering, fishbone diagram, and FMEA, were applied to identify an initial list of potential CQAs and CPPs. CQAs mainly refer to quality attributes of raw material, intermediate or final product. In process optimization DOE was used to evaluate effects of the design factors on manufacturability and final product CQAs such as tablet blend flow and tablet dissolution, and establish design space to ensure the desired CQAs.

Pharmaceutical Quality by Testing

Most of the pharmaceuticals companies adopting the principles of Quality by Design (QbD) for pharmaceutical development and manufacturing. QbD enables enhanced process understanding, and a more systematic and scientific approach to development, so that better controls may be implemented. The end goal is more accurate manufacturing processes than those that typically result from traditional approaches to drug development.

Product quality is ensured by raw material testing, drug substance manufacturing, a fixed drug product manufacturing process, in process material testing, and finished product quality testing. The quality of raw materials including drug substance and excipients is monitored by testing. Quality by design integrates quality systems and risk management approaches into its manufacturing products with the goal of providing the necessary framework for implementing quality by design, continual improvement and risk management in the drug manufacturing process and also for post development changes and optimization.

If pharmaceutical companies fulfill all requirements of FDA approved specifications or other standards such as USP for drug substance or excipients, they can be used for the manufacturing of the products. Finished drug products are tested for quality by assessing whether they meet the manufacturer's proposed and FDA approved specifications.

FMEA is a systematic analysis of potential failure modes aimed at preventing failures. This is intended to be a preventative action process carried out before implementing new or changes in products or processes. An effective FMEA identifies corrective actions required to prevent failures from reaching the customer and to assure the highest possible yield, quality and reliability.

Typical specifications for an immediate release oral solid dosage form, for example, include assay, uniformity, impurities, moisture, and dissolution. Under the current period, the specification is tight because it is used to assure consistency of manufacturing processes. So the drug manufacturers are tested few tablets out of several million that usually expected to conduct extensive

in process tests, such as blend uniformity, tablet hardness, etc; to ensure the outcome of in-process testing also meets the FDA approved in-process testing specifications. Thus the combination of fixed manufacturing steps and extensive testing is ensures quality system. All products are treated equally without regard to the risk to the consumer. In summary, product quality and performance are, in the traditional framework, achieved predominantly by restricting flexibility in the manufacturing process and by end product testing.

Pharmaceutical Quality by Design

QbD is a novel approach in pharmaceutical industry. It places more emphasis on continuous improvement rather than end-product testing. The pharma industry, however, is just beginning to experience the benefits of QbD.

The Quality by Design approach requires having a sound understanding of their product in the company. QbD makes certain that the product is of predictable and predefined quality. The adoption of QbD includes defining a target product quality profile; designing the manufacturing process from basic principles with a very good understanding of the mechanism involved (Design of Experiment); identifying critical quality areas, process parameters and potential sources of variability; and finally controlling manufacturing process to achieve the most consistent quality.

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.” ICH Q6 emphasizes the role of specifications stating that “Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by regulatory authorities.” As per ICH Q8 defines that pharmaceutical 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.” Pharmaceutical QbD is a systematic, scientific, risk-based, approach to pharmaceutical development that begins with predefined objectives. QbD identifies characteristics that are critical to quality and translates them into the attributes that the drug product should possess, and establishes how the critical process parameters can be varied to consistently produce a drug product with the desired characteristics.

Under the QbD approach, pharmaceutical quality for generic drugs is assured by understanding and controlling formulation and manufacturing variables. End product testing confirms the quality of the product and is not part of the manufacturing consistency or process control.

The specification for impurities assesses another important characteristic a drug product must have to ensure its safety. Under the QbD, the acceptance criterion of an impurity should be set based on its biological safety level instead of the actual batch data. The biological safety level is generally determined by safety studies although it may be also determined by toxicity studies. It should be noted that although there is a specification for a drug product under both the QbT and QbD paradigms, the roles that the specification plays are completely different. Under the QbT, each batch has to be tested against the specification to ensure its quality and manufacturing consistency. Under the QbD, batches may not be actually tested against the specification as the process understanding and/or process control provides sufficient evidences that the batches will meet the specification if tested, which allows the real time release of the batches. Further, the specification under the QbD is solely used for the confirmation of product quality, not manufacturing consistency and process control.

Combine prior knowledge with experiments to establish a design space or other representation of process understanding. & establish a control strategy for the entire process that may include input material controls, process controls and monitors, design spaces around individual or multiple unit operations, and final product tests. The control strategy should encompass expected changes in scale and can be guided by a risk assessment. & continually monitor and update the process to assure consistent quality Design of experiments (DOE), risk assessment, and process analytical technology (PAT) are tools that may be used in the QbD process.

Aspects of QBD

Target Product Quality Profile (TPQP)

FDA published a recent guidance defining a Target Product Profile (TPP) "The TPP provides a statement of the overall intent of the drug development program, and gives information about the drug at a particular time in development. Usually, the TPP is organized according to the key sections in the drug labeling and links drug development activities to specific concepts intended for inclusion in the drug labeling."

The target product quality profile (TPQP) is a quantitative surrogate for aspects of clinical safety and efficacy that can be used to design and optimize a formulation and manufacturing process. It should include quantitative targets for impurities and stability, release profiles and other product specific performance requirements

The TPQP is not a specification because it includes tests such as bioequivalence or stability that are not carried out in batch to batch release. The TPQP should only include patient relevant product performance. For example, if particle size is critical to the dissolution of a solid oral product, then the TPQP should include dissolution but not particle size

Target Product Quality Profile (TPQP) is a tool for setting the strategic foundation for drug development - "planning with the end in mind." The target profile is a summary of the drug development program described in the context of prescribing information goals. The TPP can play a major role in the entire drug discovery and development process such as: effective optimization of a drug candidate, design of clinical research strategies, and constructive communication with regulatory authorities. TPQP is related to identity, assay, dosage form, purity, stability in the label. For example, a typical TPQP of a solid oral dosage form would include

– Tablet Characteristics
– Identity
– Assay and Uniformity
– Purity/Impurity
– Stability
– Dissolution

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Formulation by Design and Development

The availability of drug substance may influence the number of studies and therefore, product understanding. QbD should rely on the relevance of individual studies rather than the number of studies because one of the objectives of QbD is to understand how the material attributes of the drug substance and excipient influence product quality. Formulation design space would be valuable to industry if appropriate regulatory flexibility is granted.

In order to design and develop a pharmaceutical product that has the desirable TPQP, a product development must give serious consideration to the

biopharmaceutical properties of the drug substance. These biopharmaceutical properties include physical, chemical, and biological properties. Physical properties include physical description (particle size, shape, and distribution), polymorphism, and aqueous solubility as function of pH, hygroscopicity, and melting points. Chemical properties include pKa, chemical stability in solid state and in solution as well as photolytic and oxidative stability while biological properties include partition coefficient, membrane permeability, and oral bioavailability. The investigation of these properties is termed preformulation in pharmaceutical science. The goal of preformulation studies is to determine the appropriate salt and polymorphic form of drug substance evaluate and understand its critical properties.

A sound understanding of mechanical properties of the drug and excipients can be useful in developing a processing method such as granulation or direct compression, rationally selecting excipients whose properties can compensate for the properties of the drug substance. The excipients can alter stability and bioavailability of drugs, the general principles of selecting suitable excipients for dosage forms are not well defined, and excipients are often selected without systematic drug-excipient compatibility testing. To avoid costly material wastage and time delays, ICH Q8 recommends drug-excipient compatibility studies to gain early prediction of drug-excipient compatibility. Systematic drug-excipient compatibility studies offer several advantages: minimizing unexpected stability problems which usually lead to increases in time and cost; maximizing the stability of a formulation; and enhancing understanding of drug-excipient interactions that can help with root cause analysis if stability problems occur.

Identify Critical Quality Attributes, Process Parameters

The FDA has stated that "Quality by Design means that product and process performance characteristics are scientifically designed to meet specific objectives." As a direct consequence, one of the core tenets of Qbd is the requirement of detailed knowledge of the critical quality attributes(CQA) of the pharmaceutical product and the critical process parameters(CPPs) that can be used to control overall product quality. Gathering the raw data needed for this endeavor can be prohit time, labour, cost intensive without employing Design of Experiment (DOE) approach, also known as Factorial Experiment Design (FED). Even with DOE, a significant number of samples need to be processed, which has created a need for next generation.

A pharmaceutical manufacturing process is usually comprised of a series of unit operations to produce the desired product. A unit operation is a discrete activity that involves physical changes, such as mixing, milling, granulation, drying, compaction, and coating. A physical, chemical or microbiological property or characteristic of an input or output material is defined as an attribute. Process parameters include the type of equipment and equipment settings, batch size, operating conditions (e.g., time, temperature, pressure, pH, and speed), and environmental conditions such as moisture. The quality and quantity of drug substance and excipients are considered as attributes of raw materials. During process development, raw materials, process parameters and quality attributes are investigated. The purpose of these studies is to determine the critical raw material attributes, process parameters and quality attributes for each process, and to establish any possible relationships among them. Critical quality attributes (CQA) are physical, chemical, biological, or microbiological property or characteristic that must be controlled directly or indirectly to ensure the quality of the product. Critical process parameters (CPP) are process inputs that have a direct and significant influence on critical quality attributes when they are varied within regular operation range. Lists typical tablet manufacturing unit operations, process parameters, and quality attributes for solid dosage forms. It should be noted that the equipment maintenance, operator training, standard of operation (SOP) related to the specific product manufacturing, and facility supporting systems may link to product quality directly or indirectly.

Design of experiments (DOE) is a structured and organized method to determine the relationship among factors that influence outputs of a process. When DOE is applied to pharmaceutical process, factors are the raw material attributes (e.g., particle size) and process parameters (e.g., speed and time), while outputs are the critical quality attributes such

as blend uniformity, tablet hardness, thickness, and friability. As each unit operation has many input and output variables as well as process parameters. DOE results can help identify optimal conditions, the critical factors that most influence CQAs Based on the acceptable range of CQAs, the design space of CPPs can be determined.

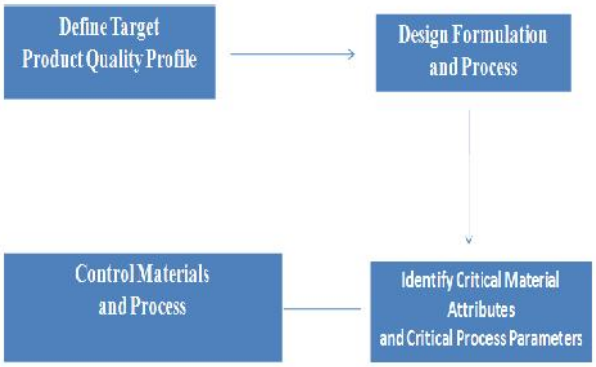
Critical Quality Attributes

ICH Q8 (R1) defines CQAs as physical, chemical, biological or microbiological properties or characteristics that should be within an appropriate limit, range, or distribution to ensure the desired product quality. CQA is used to describe both aspects of product performance and determinants of product performance. CQA is generally assumed to be an attribute of the final product, but it is also possible to indicate a CQA of an intermediate or a raw material.

Critical Process Parameters

Critical process parameter as any measurable input or output of a process step that must be controlled to achieve the desired product quality and process consistency. Process parameter be understood as referring to the input operating parameters (mixing speed, flow rate) and process state variables (temperature, pressure) of a process or unit operation. Under this definition, the state of a process depends on its CPPs and the CMAs of the input materials. Monitoring and controlling output material attributes can be a better control strategy than monitoring operating parameters especially for scale up. For example, a material attribute, such as moisture content, should have the same target value in the pilot and commercial processes. An operating parameter, such as air flow rate, would be expected to change as the process scale changes.

A parameter is critical when a realistic change in that parameter can cause the product to fail to meet the TPQP. The first step in classifying parameters is to define the range of interest which we call the potential operating space (POS). The POS is the region between the maximum and minimum value of interest to the sponsor for each process parameter. The criteria for identifying critical and non-critical parameters are that a parameter is non-critical when there is no trend to failure within the POS and there is no evidence of interactions within the proven acceptable range, which is the range of experimental observations that lead to acceptable quality. A parameter is critical when there is an observation of failure or a trend to failure predicted within the POS. If the interaction between two parameters is significant enough to predict a potential failure in the POS, then both parameters should be considered as critical. The most definitive way to identify critical and noncritical parameters is by scientific investigations involving controlled variations of the parameters. When the sensitivity of process parameters is established, this can be used to design appropriate control strategies. The set of CPP is not unique, but the chosen set must be sufficient to ensure product quality. Different sets of CPP can have several origins. For example, one fluid bed dryer may define the product temperature as an operating parameter and have an internal control system (a thermostat) that maintains that temperature, while another fluid bed dryer may have inlet air flow rate and inlet air temperature indicated as operating parameters. The batch record for the first unit might indicate a fixed temperature, while the second unit would have a design space that indicated the combination of inlet air flow rate and inlet air temperature that would insure the appropriate product temperature. Another source of differences in the set of CPP comes from the balance between control of operating parameters and material attributes.



Risk Assessment and Design Space

Quality Risk Management indicates that, the manufacturing and use of a drug product necessarily some degree of risk. The level of effort, formality and documentation of the quality risk management process should be important with the level of risk. Performing a risk assessment before pharmaceutical development helps manufacturers decide which studies to conduct. Risk assessments are often driven by knowledge gaps or uncertainty. Study results determine which variables are critical and which are not, which then guide the establishment of control strategy for in-process, raw-material, and final testing.

Design Space is considered to be a change and would normally initiate a regulatory post approval change process. As such, the Design Space will require management under a company's Pharmaceutical Quality System. The creation of a Design Space begins with the definition of the Pharmaceutical Target Product Profile (PTPP), which identifies the desired performance characteristics of the product. The quality of raw materials should be assessed, and any critical quality attributes identified. As development continues, additional risk assessments can occur that define subsequent experiments that lead to an understanding of the interactions between different attributes and process parameters. In addition, multivariate models can be used to build the Design Space.

The Design Space is linked to criticality through the results of risk assessment, which determines the associated CQAs and CPPs. The Design Space also contains the proven acceptable ranges (PAR) for CPPs and acceptable values for their associated CQAs. Normal operating ranges are a subset of the Design Space and are managed under the company Pharmaceutical quality System. The Design Space may also contain operating ranges for process parameters classified in the intermediate criticality category discussed previously. Information regarding site and scale of manufacture may also be included, depending on the quality of the process knowledge upon which the Design Space is based. A design space may be constructed for a single unit operation, multiple unit operations, or for the entire process. A design space is a way to represent the process understanding that has been established.

Developing the control strategy

The development of a control strategy will be assurance of product safety, efficacy and quality, the Control Strategy may also ensure the meeting of other business objectives such as operator health and safety, and protection of the environment, manufacturability, and supply related issues, efficiency. Development of a Control Strategy for a product will therefore be a structured activity involving a multi-disciplinary team of experts. This team may include representatives from formulation development, drug substance development, process development, analytical development, QC, QA, Regulatory Affairs and manufacturing. Existing risk assessment tools such as HACCP (Hazard Analysis and Critical Control Points), 'Worst Outcomes Analysis' FMECA (Failure Mode Effects and Criticality Analysis) can provide a framework for Quality Risk Management. A Control Strategy and a product release strategy are not the same, but demonstration of adherence to the Control Strategy would support the product or batch release strategy.

Control of input material attributes

Manufacturing processes may be caused by variability in the drug substance and raw materials and their attributes, when linked to a CQA. The input attributes not only chemical but also physical material attributes and their variability need to be understood. For example, for an oral solid dosage product, input attributes such as participle size distribution, particle shape distribution, density, surface area, , friction, elastic modulus, surface energy, flow, cohesiveness, amorphous content, solubility, and static charge should be assessed. A interrelationship between the product CQAs and the input material attributes should enable identification and understanding of the most critical material attributes and their impact on the product CQAs. Controlling the variability of input quality materials can be managed in different ways, e.g. by functional specifications. By applying PAT tools such as NIR (Near Infrared) spectroscopy, drying can be monitored on-line and the drying process controlled to the end-point with a closed feed-backward control loop in place. In many cases the variability in a material input can be managed by operating the process conditions differently within the Design Space.

In-process controls

This include all controls that need to be performed during processing, including control of Critical Process Parameters, in-process material attributes and components, as well as equipment and facility parameters that must be monitored or controlled to achieve the product CQAs. Controlling the Critical Process Parameters during processing is important as they have a direct impact on the CQAs. Which parameters to monitor or control is the outcome of Quality Risk Management (QRM) activities aimed at mitigating the risks arising during manufacturing.

Conclusion

The conclusion of QbD is focuses on building quality into the product and manufacturing processes, as well as continuous process improvement – reduction of variability. The backbone for Pharmaceutical companies is quality of the products. PQS should facilitate continual improvement and help to: "Identify and implement appropriate product quality improvements, process improvements, variability reduction, innovations and pharmaceutical quality system enhancements, thereby increasing the ability to fulfill quality needs consistently. For quality improvement efforts, products should already be in compliance with their specifications and process improvement steps should be within the original "design space".

Examples of Improvement of quality is include adjusting a set point of a process, advanced control techniques ,new equipment of the same design, re-designing a process step ,changing a working process, simplifying documents, automatic a process, installing on-line measurements, removing a unit operation, changing the design space and updating the Control Strategy.

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