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QbD- QUALITY BY DESIGN ANALYTICAL METHOD DEVELOPMENT AND VALIDATION-AN OVERVIEW

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ABSTRACT

The idea of "Quality by Design" (QbD) has attracted much focus among the prescription drugs sectors for sustaining Quality. It acts as a link between the pharmaceutical sector and drug regulating agencies, supporting the shift to a proactive, scientific, risk-based, and integrated method for approaching pharmaceutical product creation. It mostly entails creating formulas and manufacturing procedures to ensure product quality. The design, development, and production of high-quality pharmaceutical goods are areas where QbD can add value. FDA, the Food and Drug Administration & the International Conference of Harmonization (ICH) are heavily promoting quality by design (QbD) to reduce the rising costs of development and regulatory barriers to creativity and innovation. The ICH guidelines, the three components that make up QbD's foundation are, (quality risk management) Q9, Q10 (quality systems), and (pharmaceutical development) Q8. As part of the (QbD) approach, the formulation and process are designed and developed using the quality target product profile (QTPP), key quality attributes (CQA), risk assessment, and life cycle management. This review focuses on the basic concept of (QbD) its applications, ICH guidelines, the process of the development of an analytical method using the QbD approach, various RP-HPLC method creation and verification by using the QbD approach, different analytical techniques using QbD and method validation regulation.

Keywords: (QbD) Quality by Design, ICH Guidelines, Quality, Method of Analysis, RP-HPLC, Validation.
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INTRODUCTION

The pharmaceutical sector includes research, development, and manufacture of drugs and treatments. In the pharmaceutical industry, "quality by design" has evolved as a critical concept. It was started by the USFDA. QbD's primary goals are to design an appropriate process and understand process performance in order to achieve the desired product performance. Along with safety and effectiveness, quality is a critical condition for any entity to qualify as a drug and be granted regulatory clearance.[1] Global symposium on standardizing technical specifications for human use pharmaceutical registration. The ICHQ8 (R2) Guideline describes (QbD) as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process. “Regulation predication on thorough investigation and prudent risk mitigation." ICHQ8 (R2) guidelines. "The compatibility of either a drug substance or a drug product for its intended use" is an indicator of quality. The phrase encompasses attributes such as purity, strength, and identity (ICH Q6A).[2] Dr. Joseph M. Juran, a pioneer in quality, was the first to develop the concept of design excellence Dr. Juran contends that quality needs to be incorporated into a bulk of quality issues that occur in products from the beginning and problems are caused by bad product design. Woodcock defines an excellent medication product as one that is uncontaminated and consistently provides the desired therapeutic outcome specified. A contaminated-free medication product that achieves the intended therapeutic effect is considered high-quality, according to wood cock on the label.[3] Quality by design (QbD) ensures the product's in vitro performance, which is then extended to in vivo. QbD and product performance are consequently linked. By providing recommendations for creating manufacturing procedures and formulation, QbD is a step toward pharmaceutical development that assures pre-planned product standards. It has provided the solution to assist industry and regulatory bodies in transitioning to a more proactive and scientific approach over time.[4]

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Understanding how the product is affected by process and formulation quality characteristics is an important aspect of quality by design. Following that, these characteristics should be improved in order to enable online monitoring of these parameters during the production process.[5]

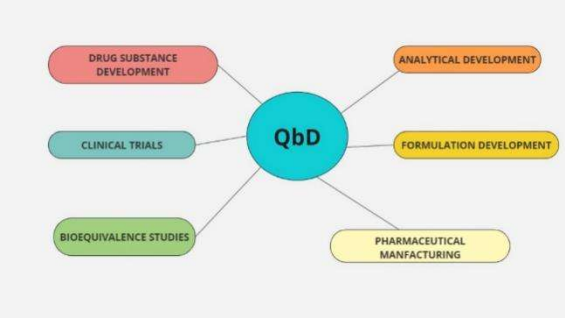

Fig.-1: The Product Development Life Cycle in QbD

Designing For Pharmaceutical Quality-Goals[6]

Designing for Pharmaceutical Quality aims to meet clinical activity-based product quality criteria. Improve product and process design, knowledge, and control to enhance efficiency and reduce faults. Improve pharmaceutical production and development. Enhanced root cause analysis and post-approval change management are needed. Put batch failures to rest. Minimizes deviations and expensive inquiries. Guarantees regulatory compliance.[6]

Investing in Organizational Learning Can Yield Future Qbd Advantages[7]

The science of QbD is remarkable. Development alternatives are optimized. Empowering technical personnel.

Analytical Method Development Using the Qbd Approach

A target profile for analysis. An important feature of quality. Evaluation of risk. Region of method operational design. Control strategy. Life cycle Management.[8]

A Comprehensive Target Profile (Atp)

The analytical target profile (ATP) is a collection of standards that specify the concentrations at which analytes are measured, as well as the accuracy or precision of the methods used to estimate matrix analytes or calculate concentration ranges. Following ATP identification, relevant analytical methods are chosen based on the identified ATPs; for example, HPLC is a more reliable approach than GC or UV for drug impurity and stability profiling. The third phase in method development is risk assessment, which examines all parameters from sample preparation to method conclusion (data analysis). To create the design space, elements with a stronger influence on key quality attributes (CQAs) are identified.[9]

Critical Quality Attribute (CQA)

Based on the ICHQ8 (R2) guideline an essential component of quality, or critical quality attribute, is a microbiological, physical, chemical, the biological, trait or characteristic that must be within a specific range, limit, or distribution to provide the specified level of product caliber.[2] CQA is frequently connected with pharmaceutical goods, in-process materials, prescription components, excipients, and intermediates.[2] Analytical methodologies for CQA may differ. The GC processes comprise the oven and program temperature, injection temperature, gas flow rate, sample diluents, and concentration.[8] MP buffer, mobile phase PH, selection of column, Organic modifier, and the resolution method are all part of the CQA for the HPLC operation[8].CQA for the HPTLC technique consists of TLC Plates, Mobile Phase, injection volume and concentration, plate development time, and a regent for color development and detection.[8]

Risk Assessment

The quality risk management system captures all of the process and product information, as well as the total risks that the Qbd components and their consequences provide. Once the process, product characterization, and validation cycles are completed, the risk associated with a high-quality product or production capacity should be limited and acceptable.[10] According to ICHQ8 (R2), probability assessment

is an essential scientifically based method used in quality possibility management (ICH Q9) that may assist in determining which material features and operational factors may have an influence on product CQAs. Prospect assessments are often undertaken early on in the process of developing pharmaceuticals and are repeated when new data and knowledge become available.[2]

Method Operational Design Region (Modr)

The important method input variables' operating range or MODR (almost equivalent to CQA), is what yields outcomes that often satisfy the ATP objectives. The approach operational design region is the following phase once the method development and risk assessment are completed. MODR is used on a regular basis to create operational areas. The MODR is a multivariate, risk-based, science-based tool for determining the influence of several variables on the effectiveness of the technique. It regulates critical processes RRT, RRF, and system compliance, for example. One can also define the MODR during the stage of developing the approach, which might be a source of dependable also sensible solutions in compliance with the ICHQ8 standards on the need for "design space" in product creation.[11]

Strategy of Control

A predefined set of control (s) for each conceivable variation (s) ensures both the transfer of an analytical method and its routine use. This may be accomplished by regularly monitoring the system appropriateness parameters or CMAs. Control strategy can alter during a method's existence and is not always a one-time activity performed during method creation. It is important to remember that the control technique utilized in the QbD approach is identical to that traditional control strategy. Method controls must be designed to ensure that the method's aim is linked to its performance.[12]

Life Cycle Management

Changes to design-space procedures will not have to be evaluated or authorized under the QbD paradigm. As a result of fewer post-approval submissions, process consistency, and throughput gains may be realized across the product life cycle.[1]

Qbd Approach Development and Validation of Rp-Hplc Method

It researched the tenofovir Disoproxil Fumarate analytical RP-HPLC method development and validation using a QbD approach in Dose Form. In this work, the author outlines the objective of detecting the concentration of bulk and tablet dose forms of tenofovir Disoproxil Fumarate by developing a simple, sensitive, and reproducible spectrophotometric approach. Design quality (QbD) is the pursuit of desired and planned criteria to achieve a certain predictable quality. Understanding components and the consequences of their combined use across a certain set of trials is an extremely useful QbD component. The Creation of an extensive, risk and science-based RP-HPLC is described in the current work technique for the analysis of Tenofovir Disoproxil Fumarate tablets using a quality-by-design approach and active pharmaceutical ingredient (API) methodology. An efficient experimental design is presented based on a thorough reconnaissance of the essential elements of the RP-HPLC process (column and phase of mobility). Furthermore, the findings for accuracy, ruggedness, and robustness (1% for system precision and 2% for other attributes) were all within acceptable levels. Tenofovir Disoproxil Fumarate may be regularly evaluated in quality control labs using the indicated method.[14] Performed research on the use of QbD in the creation of analytical methods for anti-psychotic drugs. A straightforward and reliable analytical HPLC method for the crucial separations can be created scientifically using the QbD approach. Utilizing Design-Expert Software, Version 9, the author of this study devised a reliable technique for the degradation of risperidone and benzoic acid. The flow rate (A), wavelength (B), and buffer pH (C) were three independent factors that were utilized. The software recommended a total of 27 experimental runs to examine the interaction between each level and the formulation characteristics, as response variables (dependent factors), utilizing the tailing factor (5%) and theoretical plate USP(NTP) numbers peak area (R1) (R3) taken into account. In accordance with ICH recommendations, the approach was validated. Analyzing samples comprising a mixture of medicinal products and excipients allowed researchers to gauge the method's specificity. With the currently developed chromatographic conditions, the assay for the commercially available oral solution was established, and it was discovered to be more accurate and reliable. It was discovered that the sensitivity and RSD percentages fell between 100 1.5% and 2,

respectively. It demonstrates that the process abides by the ICH recommendations. The results of the stability testing ranged from 99.5 to 101.5%. Per ICH recommendations, the target degradation for the assay method's capacity to indicate stability was tested in the current investigation. The degradation products at the medication RT did not cause any interference peaks to be discovered. Automatic prediction and testing of speed and resolution-optimized analytical techniques that distinguished all the drug peaks was made possible by Design Expert.

In order to ensure that the greatest amount of pure fractions could be recovered, analytical preparation for scaling up the drug peaks was effective[15] conducted analysis using a QbD approach, and an RP-HPLC technique was developed and validated for the simultaneous measurement of xipamide and valsartan in human plasma. A novel RP-HPLC technique was created that is quick easy to use and sensitive using the QbD methodology, as explained by the author of this article, in order to ascertain the levels of valsartan with xipamide in human plasma. Detecting wavelength, pH, flow rate, MeOH percentage, and other four independent parameters were screened using a partial factorial arrangement. All that was significant, according to an ANOVA, were the flow rate and the MeOH percentage. The chromatographic condition was optimized using a central composite design. The procedure was ascertained by using a PH 3(64.5:35.5 v/v) isocratic mobile phase consisting of MeOH and 0.05M KH2Po4 buffer, a flow rate of 1.2 mL/min, UV detection at 240nm and a 10-microliter injection volume using the BDS hypersil c8 column (250x4.6mm, 5m). Later, the FDA authorized the method for the clinical assessment of the two drugs in human plasma based on the results of pharmacokinetic and bioequivalence simulation studies that would take place later. The determination coefficient(R2) for the standard curves of both medications was 0.999 and the range of average recoveries was between 99.89 and 100.03%. The Pharmaceuticals standard curves were linear over the range of concentration of 5-100mg/mL. Good predictability and robustness were demonstrated by the suggested approach.[16]

QbD Integration with Analytical Measurement Techniques[17]

The Analytical Technical Group (ATG), (EFPIA) the European Federation of Pharmaceutical Industries and Association, and US pharmaceutical producers and researchers have all given specific instructions on how to employ QbD with analytical techniques. QbD can be used in conjunction with a range of analytical techniques, which includes the following: Chromatographic methods like HPLC (for method development, stability studies, and the detection of contaminants in medicines). Cutting-edge techniques like mass spectrometry, capillary electrophoresis, and ultra-high-performance liquid chromatography. LC-MS is a technique with two hyphens. Biopharmaceutical processes. Chemical identification and quantification are accomplished via vibrational spectroscopy, such as the UV method. Dissolution studies. Karl Fischer titration for determining moisture content. Examining genotoxic impurities.[17]

Applications of QbD[18]

QbD is used extensively in the pharmaceutical sector. These are a few of the applications.

Polymeric surfactants and crystallization inhibitors are being used in pharmaceutical quality control to improve Class II BCS drug solubility and dissolution. Controlled-release tablets are being created. Application of QbD to Analytical Separation Method Development: Analytical separation techniques are used for quality control of API and drug products, making it vital to apply QbD to their development. The study methods employed included HPLC and Capillary Electrophoresis (CE).[18]

Regulation For Method Validation[19]

Overall, validation of an analytical technique is always carried out in accordance with ICH Q2 (R1) standards according to normal operating circumstances (NOC) or the so-called optimum state, which includes a collection of parameters at a specific time. A combined precision, as well as accuracy analysis at a number of factor locations inside the chromatographic separation space (from MODR), can be used to undertake process confirmation as well as to method validation in accordance with regulatory advice. The best possibility that the approach will be able to satisfy the ATP criteria may be represented by this multipoint verification within MODR. This multipoint verification should be carried out beyond the standard robust test limitations at more notice that the points are from the MODR; however, there are more than two points with both deviations. For example, the temperature of a column can be verified to

be between 35 and 45 degrees Celsius. The pH of the mobile phase can be as low as 0.3 units, and the percentage of aqueous or organic components may be verified up to 5%. With a target value of the variable, the verification, as well as validation tests, must demonstrate that they are robust throughout the parameter ranges from low to high. If the target buffer concentration is 15 mm, for example, the robust check needs to be performed from 10mM (low) to 20mM(high). The technique's operational range for buffer concentration can be 10–20 mM, given the specificity is being demonstrated if the performance parameters are satisfactory and comply with ATP.[19]

CONCLUSION

As the pharmaceutical industry continues to innovate, (QbD) is gaining prominence as a crucial and widely adopted strategy. It enhances manufacturing efficiency while ensuring patients receive top-notch medications. QbD, alongside its associated tools, underscores the importance of integrating quality considerations into modern production processes, leading to cost and time savings. Moreover, QbD extends its application to various biotechnological products like monoclonal antibodies, vaccines, and enzymes. This innovative QbD approach promises increased adaptability for future regulatory frameworks. Additionally, Quality by Design has transcended its origins in medicine to become a universally applicable manufacturing methodology.

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CONFLICT OF INTERESTS

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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