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REVIEW ARTICLE

An Overview of Analytical Quality by Design in Pharmaceuticals

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ABSTRACT
In addition to efficacy and safety, quality is a crucial requirement for any molecule to be qualified as a medicine and receive regulatory approval. "A scientific method to pharmaceutical development that emphasises process and starts with specified goals and understanding of the process, supported by sound science, and effective risk management," is how ICH recommendation Q8(R2) defines quality-by-design (QbD). Beginning with product creation, understanding the production process, essentially creating quality in the product rather than testing it. During the design it is essential for a product's development to define the Quality Target Product Profile (QTPP), the target product profile (TPP), desired product performance profile (DPPP) and critical quality attributes (CQA). Currently, AQbD stands for the notion of QbD applied to the creation of analytical techniques (Analytical Quality by Design). It enables analytical techniques to roam entire region of method operable design (MODR). Because of robustness of the method well within the area, analytical methods created utilising the AQbD approach have a lower rate of Out-Of-Trend (OOT) findings and Out-Of-Specification (OOS) results than current methods. Analytical quality by design (AQbD), a component of managing risk, pharmaceutical quality system and pharmaceutical development, is a current trend in the pharmaceutical business (ICH Q10). This essay provides information about Pharmaceutical QbD, Analytical QbD, and uses of QbD and AQbD to guarantee pharmaceutical quality.
Keywords: *Quality-by-design, Analytical quality by design, Software's, Fusion, Design Expert.*

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INTRODUCTION

Pharmaceutical companies are always seeking for ways to enhance the effectiveness, quality, and safety of their products. But recent drug recalls, pricey industrial failures, scaling up issues, and regulatory hurdles have posed serious problems for the industry. With little knowledge, the process and important process parameters, previous methods mostly rely on end-product testing to assure the product quality and performance, thus regulatory authorities' attention is focused on process variance and the supporting process-control mechanisms. A methodical development strategy that starts with predetermined goals, places a focus on product and process knowledge as well as continuous improvement, and is supported by strong science and first-rate risk management [1].

Historical Background of QbD:

Table 1: Historical Background of QbD

Year	Activities
1950	Operation windows
1970	QBD created by Joseph M Juran
Sept 2002	QBD concept integrated by USFDA in cGMP
Sept 2004	USFDA release final report in "Pharmaceutical cGMP"
Sept 2004	USFDA Guidance for Industry: PAT

Nov 2005	ICH: Q9 Quality Risk Management
Oct 2006	Merck & Co's Januvia: first FDA approved product
June 2008	ICH: Q10 Pharmaceutical Quality System
Nov 2009	ICH: Q8(R2) Pharmaceutical Development

Introduced by FDA in 2002

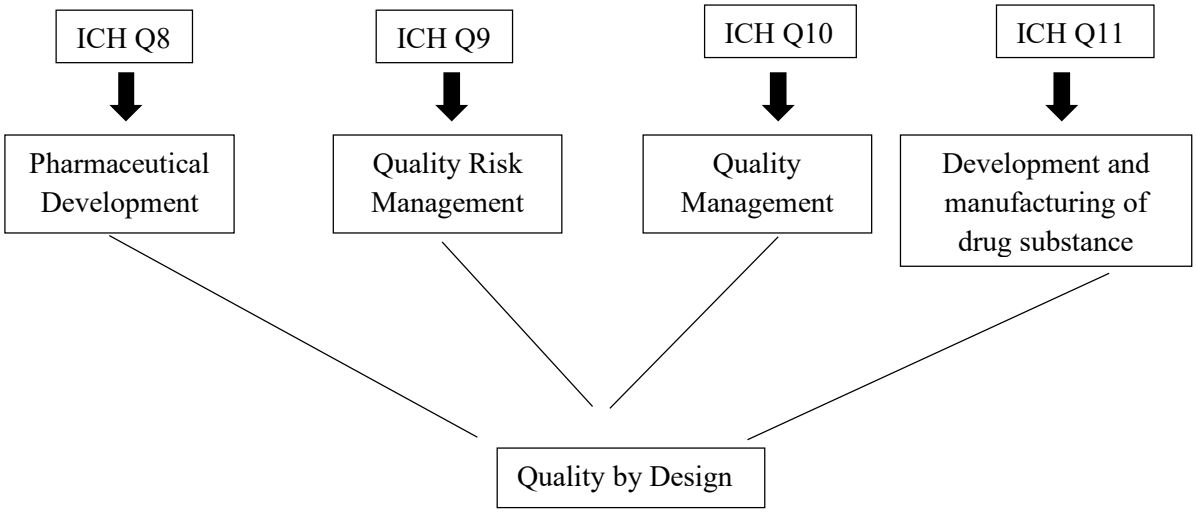

Figure 1: ICH guidelines For Qbd

The revolution in quality thinking:

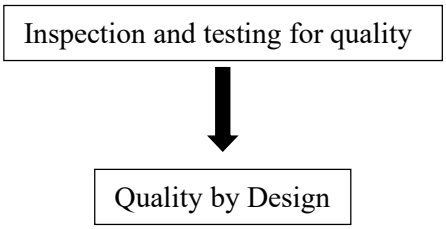

Figure 2: Concept of Qbd

WELL-DESIGNED PRODUCTS AND PROCESSES ENSURE QUALITY

Benefits of QbD [3]:

- Avoid regulatory compliance issues; get rid of batch failures.
- Reduce deviations and expensive investigations.
- A system that is effective, flexible, and agile should be implemented.
- Building a scientific knowledge base for all products, decreasing costs, project rejections, and waste
- enhancing communication with business on topics relating to science
- Ensuring reliable information
- Incorporating risk reduction
- Reducing finished-product testing
- Making release decisions more quickly is only one example of how to increase manufacturing efficiency.

KEY ELEMENTS OF QBD

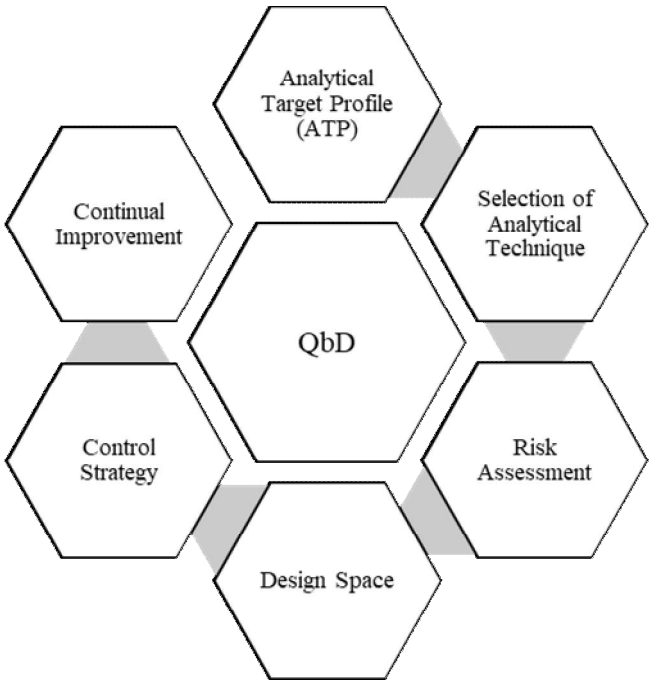

Figure 3: Key Elements of Qbd[2]

Analytical Target Product Profile (ATPP) [4]:

ICH Q8 R (2) recommendations refer to ATP as the first stage in considering intrinsic variability, systematic variability, and method appropriateness for developing methods. Despite analytical requirements the approach is most likely to undergo several changes throughout method development due to inadvertent deviations, ongoing development initiatives, requirement to use the procedure and/or method in a different context. A key component of the ATP is determining and choosing the method's target analytes (products and contaminants) that are probably have an impact on the method's performance at any point in its development. API and contaminants, the kind of analysis method, analyst, laboratory setting, equipment, and operating a method could all be target. The ATP specifies what the technique must evaluation (i.e., acceptability standards) and at the measurement's level is necessary qualities of the performance level, such as range, accuracy, precision, sensitivity, as well as the related performance criterion). Typical ATPs of a device like an LCMS/ MS might include noise, column temperature, flow rate, buffer pH, heat block temperature, etc.

CQA (Critical Quality Attributes) [2]:

To assure the required product quality, a biological, chemical, physical, microbiological trait (CQA or CPA) should fall in the proper limit, range, or distribution, according to ICH Q8 (8). 16 The analyst must in this step determine the crucial technique parameters that directly influence the performance of method. The CPAs will vary depending on the job. The three categories of critical method parameters (CMPs) are parameters pertaining to the analyte, parameters pertaining to the instrument, and parameters pertaining to the operating environment. Detector selection, sampling, standards, sample preparation, mobile phase composition, pH and flow, chemicals, column chemistry, column temperature, detector selection, etc. are examples of typical CPAs for chromatographic investigations. For the characteristics, CQAs (responses) include resolution, retention duration, tailing factor, limit of detection, and robustness. CQA is defined in terms of chemical and physical characteristics of drug ingredients, contaminants, including pH value, solubility, boiling point, polarity, charged functional groups solution stability.

Risk Assessment [2]:

The ICHQ9 guideline states that this is a methodical process for assessing, managing, communicating, and reviewing quality risk during method development. Reaching a level of confidence in the method's dependability requires completing this phase. After identifying the ATP and CPA, AQbD emphasises a thorough risk evaluation of variables which results in technique variation, including analyst methodologies, instrumental design, measurements, method variables, sampling design, sample

preparation, and environmental elements. Risk evaluation may be done within three parts, namely risk identification, risk analysis, and risk evaluation, as per ICH Q9. Risk evaluation may be done at any procedure development stage, even during ongoing method observation.

Risk Identification [4]:

Fishbone Ishikawa Diagram By classifying various components according to their sources and determining the causes and effects of chosen variables on a method's effectiveness, the risk can be recognized using an Ishikawa Fishbone diagram.

Risk Analysis [4]:

Risk analysis that can be carried out using the Failure Modes and Effects Analysis and Relative Risk Matrix Analysis methodologies. Analysis of the Relative Risk Matrix Sorting the chosen ATPs into low, medium, and high-risk categories on the CPA is the first stage in the relative risk matrix study. These risks could be related to the way an instrument is used, the properties of the reagent, the cycle duration, etc. There is no need for additional research because of the low dangers. The medium- and high-risk elements are given more focus, which is unsatisfactory because more research is required to minimize the risk. Another approach to risk analysis is failure mode analysis. Based on severity, likelihood of occurrence, and detection, the risks are assigned a number in this process, which when multiplied yields the Risk Priority Number. The method attributes are then represented as x-axis of a bar graph with RPN as the y-axis. According to RPNs, all the elements are listed on a Pareto chart in decreasing order, with High-Risk Elements being labelled as "Critical." Method characteristics with the RPN values greater than 25 are assigned top priority between all hazards; they ought to regard as the most important API material qualities that need to be regulated and/or optimised.

Method Operable Design Region [2]:

An organised sequence of tests called a MODR is used to test all potential components concurrently, methodically, and quickly by making deliberate modifications to input elements in order to uncover causes for substantial changes in output responses. The establishment of a method operable design region (MODR) when the approach was being developed stage can also be a source for reliable and economical methods. The important method input variable's operating range determines whether outcomes consistently satisfy the ATP's stated objectives. Without having to resubmit to the FDA, MODR enables flexibility in a number of input process variables to deliver predicted method performance standards and method response. Once this has been established, the proper method controls can be implemented, method validation and verification can proceed. If there are more than 4, the important factors must first be eliminated by screening designs before the factors can be optimised by optimization designs. The optimization designs can directly optimise it if there are fewer than four elements.

Table 2: Comparison of Current Approach and Qbd Approach [5]

S N.	Current Approach	QbD Approach
1	Through testing and inspection, quality is ensured.	Quality is designed into the process and into the product and is based on scientific knowledge.
2	It only contains data-intensive submissions with fragmented information and no comprehensive picture.	It contains knowledge-rich submissions that demonstrate a comprehension of both the product and the process.
3	Any specifications in this instance are dependent on batch history.	In this case any criteria based on the performance requirements.
4	The process is locked here, which prevents changes from happening.	Here, the design space is flexible, allowing for ongoing refinement.
5	Focusing on reproducibility, it frequently avoids or disregards variation.	It emphasizes robustness, which recognizes and manages variation.

STEPS IN QbD PRODUCTS [6]

1. **Development of a Novel Molecular Entity:**

- Preclinical Research
- Nonclinical Research
- Clinical Research
- Scale-Up
- Market Submission Approval

2. **Manufacturing:**

- Design Space
- Process Analytical Technology

- Real-Time Quality Control

3. Control Strategy:

- Risk-Based Decision-Making
- Continuous Improvement
- Product Performance

QbD BY PHARMACEUTICALS [7]

The pharmaceutical industry places a strong emphasis on quality, but it has not kept pace with other industries in terms of productivity and production efficiency.

The pharmaceutical industry's current scenario is as follows:

- Offline analysis for ongoing- need-based projects
- Cost of revalidation.
- Unpredictable Scale-up difficulties.
- Product standards as the primary control method.
- Inability to comprehend mistakes.

A methodical strategy for development:

- It begins with predetermined objectives.
- Process control.
- a focus on comprehending products and procedures

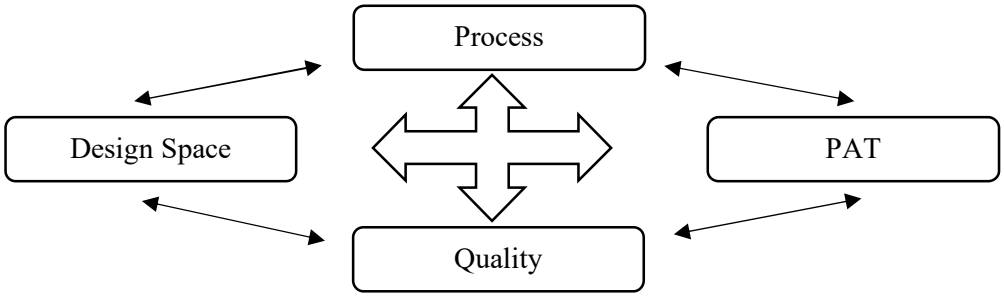

Figure 4: Interrelation between Process, Design Space, Process Analytical Technologies and Quality [7]

APPLICATIONS OF QBD [7]

A thorough, methodical approach to the development and production of pharmaceuticals

When compared to the conventional technique, QBD's advancements in pharmaceutical development and production make sense.

Table 3: Features of Traditional and Qbd Approach [7]

Features	Traditional	QbD
Pharmaceutical Development	Empirical	Methodical, multivariable research
Manufacturing Process	Fixed	Flexibility in the design space, potential for inventiveness
Process Control	Process evaluation for wide or slow response, offline analysis, and go/on-go	PAT is used for real-time feedback and feed forth.
Product Specification	The primary method of quality assurance; batch data-based	Based on the targeted product performance, a component of the entire control strategy
Control Strategy	Primarily through finished-product, intermediate-product testing	Risk-based, transferred upstream under supervision, and real-time release
Lifecycle Management	Reaction time issue, OOS, need for modifications made after approval	Enabling continuous improvement in the design space

Application of QbD in analytical methods of measurement [8]:

QbD stands for "Quality by Design," which is based on science and evaluation process and does not always imply less analytical testing. Pharmaceutical industries are adopting this notion of QbD since it enables the development of robust and durable methods that aid in compliance with ICH guidelines. This strategy

encourages ongoing method development. Despite not being used by all pharmaceutical firms, it may do so in the future since regulatory authorities may make it mandatory. Due to its many advantages and simplicity of compliance with the regulatory bodies, this approach may be adopted voluntarily by industries. The Association and European Federation of Pharmaceutical Industries (EFPIA), the Analytical Technical Group (ATG), and Pharmaceutical Research and Manufacturers of America (PhRMA) have all provided clear ideas about how to use QbD alongside analytical methods. QbD can be used with a variety of analytical techniques, such as

- HPLC and other chromatographic methods (For method development stability studies, and the identification of contaminants in medications).
- methods, such as LC-MS.
- Complex procedures including capillary electrophoresis, UHPLC, and mass spectrometry.
- Karl Fischer titration to calculate moisture content.
- Vibrational spectroscopy, including the UV technique, for the identification and measurement of chemicals.
- Biopharmaceutical procedures
- Studies on dissolution

ANALYTICAL QUALITY BY DESIGN

- Reliable on science and effective risk management, analytical QbD is a comprehensive, and proactively development using analytical techniques that emphasises the method's declared goals at the outset method knowledge and method control.
- Due to increased method resilience and toughness, analytical techniques created utilising a QbD methodology result in fewer out-of-trend and out-of-specification outcomes. QbD implementation in procedures of method development by the pharmaceutical industry, therefore it is regarded as best practise.
- The performance of a technique outside of the R&D facility where it is produced may not be guaranteed by conventional methods for method development and validation (such ICH recommendations or FDA guidelines of method validation). Additionally, the old methodologies do not examine how method enhancements might be introduced during the course of the medicine or pharmaceutical product's life cycle [9].
- The significant factors in an analytical procedure are frequently unknown or poorly understood, which makes it possible that they are not properly managed.
- Conventional methods revolve around a single validation test conducted under carefully monitored circumstances, which is then supposed to guarantee future method performance throughout the product's lifespan.
- At the conclusion of the validation process, robustness tests are frequently conducted using a univariate technique without taking into account the interacting effects.
- Traditional methods do not help to assure continued evaluation of method performance throughout everyday use and provide little emphasis on the needs of the end users. Since any changes will need to be approved by the registered methodology, making enhancements to a method created and validated using these conventional methods is more challenging and can impede ongoing improvement.
- A significant hurdle to bringing enhancements to analytical methods after first licensing clearance is the standard way to method validation as well as the concomitant regulatory requirements. On the other hand, the QbD strategy fosters improvement, guarantees product quality, and yields benefits over the whole analytical method lifecycle.
- The creation of analysis techniques that are suited for the task at hand is a key component of improved pharmaceutical procedures that incorporate QbD concepts in order to provide both process and product knowledge as well as a clearly defined overall control plan.
- Modern pharmaceutical development all across full control strategy benefits greatly from the understanding of products and processes brought about by analytical approaches [2].

The advantages of developing and validating a method using the concepts of analytical QbD are:

- The end user is taken into account when developing methods.
- We can develop stronger, more durable ways.
- Method transfer, change control, and method validation are all done using a science- and risk-based approach.
- We may take advantage of increased regulatory flexibility, which permits processes to be enhanced over the course of a product's lifecycle while maintaining product quality.

BENEFITS OF ANALYTICAL QbD [4]

- Versatility in analyzing API, contaminants in pharmaceutical formulations, stability samples, and metabolic products in biological samples.
- Increased comprehension and control.
- Further to the standard ICH technique of method validation.
- Lowering the variability of analytical characteristics to increase the robustness of the procedure.
- Smooth method transfers production level.
- No need for revalidation within MODR.
- To preserve the advantages of analysis characteristics in the pharmacopeial monographs and distant from Out of Specification (OOS) limitations.

STEPS INVOLVED IN AN ANALYTICAL QBD APPROACH TO THE VALIDATION AND DEVELOPMENT OF ANALYTICAL METHODS

- Identifying ATP for method is the first step in determining the analytical method performance requirements that should ideally be attained to ensure the analytical method performs as desired (taking into account structured variations, inherent variability, and system suitability).
- Calculate CPAs of the analytical method using those analytical method characteristics (ATPs).
- To ensure that the method performs consistently with such CPAs, investigate the correlation between the method's material properties and its parameters.
- Conduct several experiments to determine the critical method parameters (CMPs), critical method material attributes (CMMAs) that have the ability to significantly affect the CQAs.
- Create and put into action a CMMA and CMP control strategy.

Table 4: Steps involved in Product and Analytical Qbd [2]

S. N.	Product Quality by Design (QbD)	Analytical Quality by Design (AQbD)
1	Quality Target Profile (QTPP)	Analytical Target Profile (ATP)
2	Critical Quality Attributes (CQA)	Critical Performance Attributes (CPA)
3	Risk Assessment of Critical Material Attributes	Risk Assessment of Critical Method Attributes
4	Development of Design Space (DS) and Designing of Experiments	Development of Method Operable Design Region (MODR) and Designing of Experiments
5	Manufacturing Process Validation	Analytical Method Validation

APPLICATIONS OF AQbD [2]

- **Manufacturing Plant & Quality Control:** A thorough understanding of the product's behaviour predicted by a model using various QbD tools and adjustments to CMAs and CPPs inside the design space.
- **Analytical Research Development**: Developed level method comprehension for every significant aspect and the transfer of methods from AR&D to QC will be more flexible according to MODR.
- **Regulatory Affairs**: The approval and review processes will be made very simple and quick. Additionally, a created and validated design space will offer regulatory flexibility for change management after approval.
- **Quality Assurance:** Using quality risk management in development, batch failures will be eliminated, deviations will be minimized, and expensive investigations will become quicker, easier, and more efficient for root cause analysis.

SOFTWARE USED IN QBD

- ✓ Fusion
- ✓ DOE
- ✓ Design Expert®
- ✓ MODDE®
- ✓ Unscrambler®
- ✓ JMP®
- ✓ Statstica®
- ✓ minitab®

- **Fusion QbD [10]:**

The S-Matrix Fusion QbD® Software is an automated experimentation platform that integrates chromatography-focused and cutting-edge statistical methods completely. Fusion QbD offers every instrument and automation capacity required to successfully complete Stage 1 - Development procedures and Analytical Process Design as part of the modern Analytical Procedure Lifecycle Management approach to analytical development. This includes capability to characterize the strength of whole experimental area with multiple parameters in establishing using a real strong Design Space robustness metrics that are accepted by both the industry and the regulatory bodies and that can be utilized to evaluate every critical aspect of technique performance. Additionally, known as the technique operable design region, design space used analytically in QbD papers and guidelines.

To complement APLM Stage 2 - Process Performance Qualification, an entire analytical method experiment suite is included with Fusion QbD as well. A protocol for an experiment on analytical capability that explicitly defines the components of sample injection and sample preparation and the total technique variation, is part of the validation experiment suite. This gives the user the option to choose the most effective replication approach required to satisfy the performance requirements of the final method.

Key Benefits:

- Translates Qbd guidelines into practical tools.
- Created with working scientists and engineers in mind.
- Quantifies risk and manages risk.
- Compliant with 21 CFR p11
- ✓ Creates solid and convincing techniques.
- ✓ Incorporates Quality by Design into the process of developing HPLC methods.
- ✓ Significant time savings and increased instrument use.
- ✓ Eliminates transcribing errors; lowers risk of failure in validation and method transfer; and maintains an environment in compliance with FDA 21 CFR Part 11.
- **DOE (Design of Experiment):**
- A British statistician, Sir Ronald Fisher, developed some of the underlying ideas of optimization techniques that are today known as Design of Experiments in 1925. (DOE).
- Implementing DOE optimization strategies always includes using experimental designs, creating mathematical equations, and displaying the results graphically to show how the product response(s) change as a result of input variable (s).
- DOE incorporates experimental results into statistical equations, employs them as models to forecast formulation performance, and optimizes the critical responses by using various logical combination of formulations and process factors [11].
- DOE optimization provides a structured approach that connects numerous experiments in a logical way, resulting in the production of more accurate information from fewer trials. DoE illustrates how the system functions by considering all the many factors at once. It allows the experimenter to locate the "triumphant" combination by optimizing all the necessary replies.
- The sequential COST/OFAT/OVAT strategy to formulation/product optimization has been shown to be much less effective, efficient, inexpensive, and time-efficient than DOE's simultaneous testing approach used in parallel research. Over the past few years, there has been an increase in the application of DoE optimization techniques for both the creation and modification of new pharmaceutical formulations [12].
- **Steps involved in DOE [13]:**
- Establishing the experiment's goals.
- Pick variables (factors) in pharmaceutical products and/or processes that are known to have an impact on the goals (responses).
- Decide on an experimental strategy based on whether you want to filter the crucial factors or optimize the recognized critical variables (factors).
- Determine the magnitudes of all the factors. Choose a suitable design. Conduct the design and provide the data from the tests that were performed based on the design's values.
- Verify that the data support the experimental hypotheses.
- Evaluate and examine the findings.
- Use or discuss the results (which might inspire other tests or DOEs)

Types of Experimental Designs:

The different sorts of experimental designs can be categorized into the following broad groups according to the objectives for that we are performing the experiments:

- ✓ Comparative Designs [14]
- ✓ Screening Designs [14]

- ✓ Characterization Designs [15]
- ✓ Optimization Designs [15]
- ✓ Mixture Designs [11]

- **Comparative Designs:**

In an experimental study where one or more factors are being investigated but the main objective is to get a conclusion regarding one a priori significant factor, the relevant question is whether that factor qualifies as "substantial". In this case, you have a comparative problem. In these designs, all other elements are held constant while the concern factor is altered from a specified lower limit to a higher limit, and the reaction is measured.

- **Screening Designs:**

Out of the lengthy number of potential/possible factors/variables that could affect the pharmaceutical product CQAs, the primary purpose of the screening design is to identify the essential variables.

The major effects of each input element and variable under study in the design will be found with the aid of screening designs. The concern element or variable can then be classified as critical or not depending on the statistical significance of the primary effects. Also known as "Main Effects Designs," screening designs are.

We primarily employ a two-level factorial design with a yellow colour code (resolution IV) for the screening design, or a Min-Run Screening design. Supersaturated Response Surface Definitive Screening Designs are an additional choice.

To describe interactions and comprehend why particular factor combinations are effective, follow-up studies are required.

- **Characterization Designs:**

With the help of these designs, it is possible to characterize primary impacts, interactions, and even curvature to better understand the good or process that is being created, researched, or analyzed. We employ a two-level factorial design with a color-coded white (multifactorial) or green for characterization designs (resolution V or higher). The Min-Run Characterize and Irregular Res V designs are two other suitable two-level designs. Any two-level factorial design with center points can be used to calculate the effects of curvature.

- **Optimization Design or Response Surface Methodology Designs:**

The Optimization Design is used to consider the essential factors and variables that have been determined (either through the Screening Design or another approach). By estimating values for all potential critical factor combinations, optimization design aids in finding the ideal experimental point.

We employ surface response design that is suitable for the issue. Up to a quadratic model, common designs like the Central Composite Design (CCD) or Box-Behnken Design (BBD) work well.

Response Surface Methodologies (RSM) make it possible to estimate interactions and even quadratic effects, which provides information about the geometry of the response surface under investigation.

Higher-order models are possible with optimal designs because they are more adaptable.

- **Mixture Design:**

We can utilize these Mixture Designs to optimize the percentage of each excipient in a formulation if the sum of the excipient proportions adds up to 1 or 100%.

By modelling the reactions in terms of the relative proportions of the components, these designs generate runs. As one component is raised, the sum of other components must reduce since proportions are being used. The component proportions' total value is always constant. The very same units of measurement must be used for each component or element.

CONCLUSION

Quality by Design (QbD) is a significant and frequently employed technique in the creation of pharmaceuticals. It entails creating formulas and manufacturing procedures to guarantee the predetermined product quality.

When the QbD approach is applied during product development, patients will get high-quality drugs. Manufacturers will also see production improvements with a significant decrease in batch failures. Finally, drug regulatory organizations will be more assured of the superior quality of the goods they are expected to verify. Consequently, is a promising scientific tool for quality control in the pharmaceutical sector.

FUTURE PROSPECTS [16]

QbD is beneficial for both science and business because it helps to:

- Remove batch failures.

- Reduce variations and expensive research.
- Prevent issues with regulatory conformity.
- An investment for the future is organizational learning that helps technical employees feel more empowered and develop their decisions.

For FDA:

- To strengthen the scientific basis for review.
- To obtain a complete in regulatory filings and to offer improved coordination between review, compliance, and inspection.
- To ensure that judgements are founded on science rather than on subjective observations.
- To ensure review quality.
- To incorporate other disciplines for making decisions.
- For minimizing risks, used various resources.

For Industry:

- To ensure improved product design and fewer production issues.
- To utilize process awareness, risk mitigation, and post-market adjustments to limit the required quantity of manufacturing supplements.
- To permit the adoption of new technologies.
- To enhance manufacturing without being subject to regulatory review. Less waste will assure less bother during review, fewer flaws, and faster approvals, which could lead to a decrease in manufacturing expenses overall. The FDA contact will be improved by dealing scientific level as opposed to a level of process, enabling ongoing product as well as manufacturing process changes.

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