A comparison of the traditional approach to pharmaceutical development to the Quality by Design (QbD) approach

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Abstract

The provided text compares traditional pharmaceutical development with the newer Quality by Design (QbD) approach. Traditional methods are detailed, highlighting their lengthy timelines and high failure rates, primarily due to issues with efficacy, toxicity, and market demand. In contrast, QbD is presented as a proactive, science-based methodology focusing on understanding critical process and material attributes to ensure consistent product quality. The advantages and disadvantages of both approaches are explored, along with the impact of emerging technologies like Artificial Intelligence and Model-Informed Drug Discovery and Development on modern pharmaceutical development. Finally, the texts examine how both traditional and QbD methods affect process understanding, control strategies, risk management, and regulatory compliance.

Introduction

This project examines and compares two distinct approaches to pharmaceutical drug development: the traditional method and the Quality by Design (QbD) method. The traditional approach to drug development is a well-established process with a proven track record. The advent of the pharmaceutical industry occurred during the late 19th century, facilitated by companies with specialized knowledge in the field of organic chemistry and dyes, and after World War II, significant investment in research and development led to technological advancements. This traditional method is characterised by a lengthy and costly process that can span up to 15 years. It relies on demonstrating process reproducibility and testing to meet established criteria, with a focus on end-product testing and narrow process parameter ranges. Risk management in the traditional approach is often reactive, addressing issues as they arise.

In contrast, the Quality by Design (QbD) approach is a modern technique aimed at improving pharmaceutical development. This method prioritizes a deep understanding and control of both products and processes, relying on robust scientific principles and quality risk management. QbD begins with predefined objectives and focuses on building quality into the product from the outset. QbD promotes a proactive approach to risk management and regulatory compliance. The QbD method is designed to shorten development times and costs, improve product quality and performance, and lead to more robust and reliable manufacturing processes. This text will also consider the impact of Artificial Intelligence (AI) and Model-Informed Drug Discovery and Development (MID3), which are increasingly transforming the pharmaceutical industry. This analysis will explore how these approaches differ in their understanding of the process, control strategies, risk management, and regulatory compliance.

Literature Review

Chapter 1: Traditional Pharmaceutical Development

The pharmaceutical industry emerged in the late 1800s as a branch of the chemical industry. European companies like Bayer, Hoechst, Ciba, and Sandoz used their expertise in organic chemicals and dyes, followed by US companies like Eli Lilly and Pfizer. The pharmaceutical sector emerged, focusing on processing, packaging, marketing, and distributing drugs. After World War II, research and development (R&D) led to significant investment in penicillin and sulfa drugs, providing companies with financial resources, technological advancements, and innovative opportunities, particularly in the US and the UK (Malerba & Orsenigo 2015).

Developing a new drug is a long process that typically takes 12 to 15 years from discovery to market approval. It may also require an extra 10 years to fully understand the medicine's most effective use in clinical practice (Durcan 2008). The drug development process can be broadly divided into the following stages:

Discovery and Development: This stage involves identifying potential drug targets. Scientists gain new understanding of disease progression, allowing them to design a product to halt or reverse the effects of the target disease. They test multiple chemical compounds to find potential beneficial effects and may assess existing treatments for unexpected effects (Ilhan, 2022).

Preclinical Research ensures the safety and efficacy of the potential drug before clinical trials. It includes testing pharmacodynamics (PD), the drug's biochemical and physiological effects on the body, and pharmacokinetics (PK), the chemical pathways of the medicine in the body. This phase also involves toxicology testing (Grudzinskas, 2007). Preclinical research can be conducted in vitro (in a controlled laboratory setting) or in vivo (on living organisms). Promising drug candidates are rigorously tested in animal models to evaluate their safety, effectiveness, and therapeutic potential. Animal testing is regulated by various legislation acts and guidelines (Food and Drug Administration 2024, ICH, S4 1998). This stage determines the maximum safe dose and identifies potential side effects. Only a few drug candidates progress to the next stage. Molecules in preclinical development have only an 8% chance of becoming a registered drug (Waskiewicz, 2012).

Clinical Development is based on human testing and incorporates three phases of clinical trials. It is designed to comprehensively evaluate a new drug’s safety and efficacy. This phase is heavily regulated by legislation.

Phase I trials involve a small group of healthy volunteers to evaluate the drug's basic properties, including how it's absorbed, distributed, metabolized, and excreted (pharmacokinetics and pharmacodynamics). This phase primarily focuses on establishing initial safety and determining appropriate dosages.

Phase II trials expand to a larger group of patients to assess the drug's effectiveness and further evaluate its safety. This phase helps determine the optimal dosage and identify potential short-term side effects.

Phase III trials involve large-scale testing across diverse patient populations to rigorously assess the drug's effectiveness, safety, and overall therapeutic benefit. This phase provides crucial data for regulatory approval (Medina et al., 2024, Pracher & Zeitlinger, 2024).

Regulatory Review: After successful completion of Phase III trials, a comprehensive application is submitted to regulatory bodies like the FDA or EMA to review for marketing approval. This thorough review process ensures the drug meets efficacy and safety standards before it can be marketed. Upon obtaining regulatory approval, the drug is authorized for manufacturing and distribution (Huanbutta et al., 2024).

Post-Market Surveillance (PMS) also known as Phase IV clinical trials are conducted after a drug is approved and marketed to further investigate its properties. By studying the drug in larger and more diverse patient populations, these trials aim to identify rare or long-term side effects that might have been missed in earlier stages. They also provide valuable information for refining drug usage guidelines and developing new formulations to maximize therapeutic benefits. Post-market surveillance is vital for ensuring patient safety and monitoring the long-term effects of drugs after their release to the market in real-world settings. This continuous monitoring process complements the knowledge gained from clinical trials, which might have limitations in sample size, patient diversity, or follow-up duration (Grudzinskas, 2007).

The drug development is very comprehensive and multiphase process that transforms scientific insights from the initial drug discovery phase into medicines. Each stage is crucial to ensure successful new medications. The success of traditional approach to drug development can be attributed to well established process with proven track record and well-defined seps. It involves rigorous testing and robust regulatory frameworks with guidelines and standards to ensure drug efficacy, quality and safety.

The traditional method of drug development has proven effective, but it is a lengthy and costly process that can span 10 to 15 years and require billions of dollars in investment.

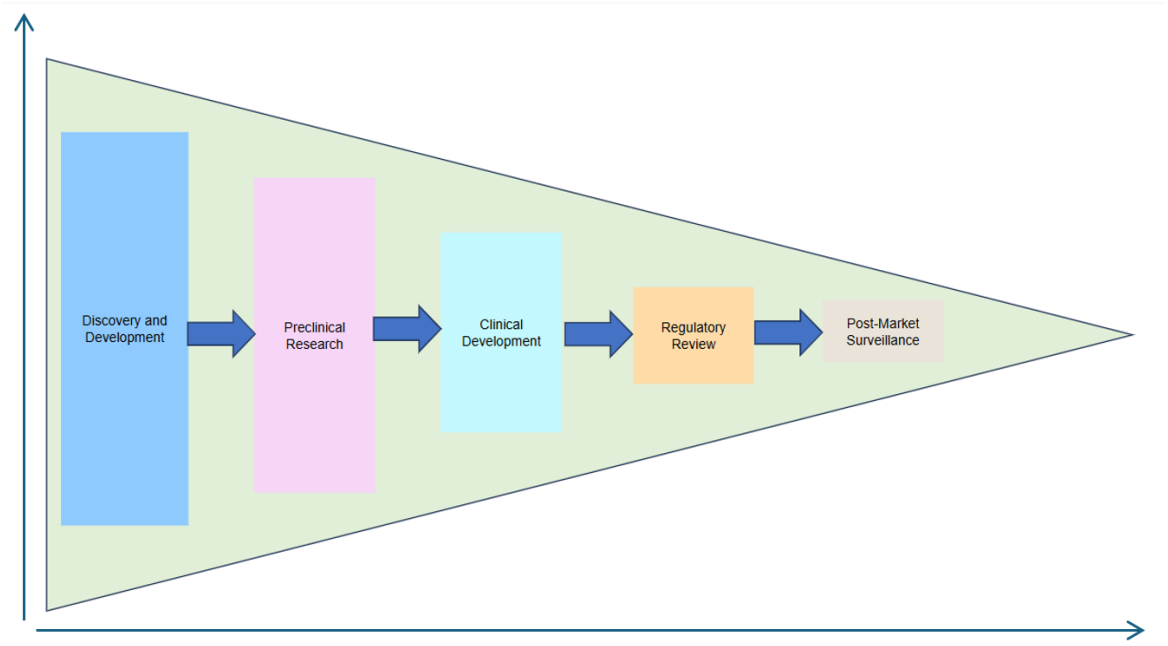

Figure 1. Visual representation of traditional drug development stages. Axis y represents number of potential drug molecules, axis x represents time.

A considerable number of experimental drug compounds are unsuccessful during clinical trials, resulting in wasted time and resources (Figure 1). Data analysis from clinical trials between 2010 and 2017 indicates that 90% of tested substances do not progress beyond the Clinical Development phase. This failure can be attributed to four primary factors: insufficient clinical effectiveness (40%-50%), unmanageable toxicity (30%), inadequate drug-like characteristics (10%-15%) and a lack of market demand coupled with subpar strategic planning (10%) (Sun et al., 2022). Traditional methods also frequently focus on a single target, potentially overlooking complex disease mechanisms (Pun et al., 2023). While animal models offer advantages, they may not always accurately predict human responses, potentially leading to safety concerns. This is because there have been instances where human participants in clinical trials have experienced harm from drugs that were considered safe based on animal studies. As a result, researchers are increasingly questioning the scientific validity of using animals in research (Van, 2019).

Chapter 2: Quality by Design (QbD)

Quality by Design (QbD) is a modern technique used to improve the pharmaceutical development process and has become a focal point in the industry1. It aims to move away from a reactive, inspection-based approach to drug development to a proactive, science-based one. QbD prioritizes upfront quality design by understanding the critical factors that affect its

quality, which can significantly improve the design, development, and production of high-quality pharmaceutical products (Sudha, 2024). The ICH Q8 (R2) Guideline defines QbD as "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". According to ICH guidelines, there are three components that form the basis of QbD: quality risk management quality systems, and pharmaceutical development (ICH, Q8 2009, ICH Q9 2023, ICH, Q10 2008). QbD considers all parameters related to formulation, production processes, and how various changes can affect product quality (Veeranti et al., 2023).

At the start QbD based process of development new drug the is establishing a Quality Target Product Profile (QTPP). It's a group of desired quality characteristics that when ideally achieved will determine quality, efficacy and safety of new drug. (ICH, Q8 2009). Those characteristics usually consists of aspects such as route of administration, dosage form, dosage strength, drug stability. An example QTPP of new developed drug is attached in Table 1.

Table 1. Quality target product profile (QTPP) for Edaravone formulations to treat motor neurone disease (MND) (O'Neill, 2024).

Attribute	Targets	Comments
Target population	Adults diagnosed with MND	Focus on adult patients due to the nature of MND.
Route of administration	Peroral and oral mucosal (e.g., sublingual)	Oral route has wide acceptance and allows for administration in a home setting without involvement of healthcare professionals, offering convenience to both patients and caregivers; sublingual tablets are small and rapidly dissolving, which benefit patients with swallowing difficulties; sublingual epithelial offers rapid absorption free from first-pass metabolism.
Target PK profile	Immediate release, high BA	Immediate release to enable rapid and complete dissolution of drug dose; BA higher than 90% by design to counter first-pass metabolism.
Dosage form	Small tablets that rapidly disintegrate in the mouth	Solid dosage form is more stable than liquid formulations, allowing for longer shelf life and reducing frequency of prescription refills. Small tablets that rapidly disintegrate or dissolve within 3 min to facilitate oral administration in patients with difficulty swallowing.
Dose	Based on clinical efficacy and safety data	Dosing regimen designed to maintain efficacy of edaravone without necessitating more frequent administration than the current regimen. The goal is to optimise patient adherence and minimise treatment burden.
Excipients and manufacturing	GRAS excipients, cost-effective production	Selected excipients are established pharmaceutical ingredients with no specific safety concerns for the MND population; manufacturing process to utilise low-cost techniques and materials.
Patient acceptability	High acceptability	Tablets designed to avoid causing difficulty in swallowing to enhance acceptance by patients in the early and mid-stages of MND. Formulation prioritises ease of administration, incorporating patient feedback to accommodate the varying abilities and preferences within MND patient group, thereby enhancing overall treatment adherence. Formulation does not have unpalatable taste.
Administration considerations	Ease of administration, minimal preparation	Tablets designed to minimise the need for manipulation for administration, particularly for end-stage MND patients relying on PEG tubes. This requires tablets to be easily dissolved in the liquid for PEG feeding without compromising drug stability or efficacy.

PK: pharmacokinetic; BA: bioavailability; GRAS: generally recognised as safe; PEG: percutaneous endoscopic gastrostomy.

Following quality target product profile characteristics new drug investigator needs to establish the Critical Quality Attributes (CQAs) of any Active Pharmaceutical Ingredient (API). The critical quality attributes are subsets of QTPP. QTPP do not change during the manufacturing process. However, characteristics like entrapment efficiency, drug release, particle size, viscosity, and many other items that can be affected by the formulation or

manufacturing process and can be considered CQAs. Critical Quality Attributes are essential criteria from the product's perspective. It can be purity, potency, particle size, shape or solubility of API. They focus on the final quality and safety of the product, which ultimately helps achieve the desired QTPPs. Critical quality Attributes are further characterised by Critical Material Attributes (CMAs), such as the chemical and biological properties of the raw materials and are crucial for ensuring the final quality of a drug product. These properties can affect the variability of CQAs and can significantly impact the final product's quality (Mohseni-Motlagh et al., 2023). Table 2. Provides examples of CQAs and CMAs.

Table 2. An example of Critical quality Attributes (CQA) and Critical Material Attributes (CMA) for hydrogel-based drug delivery system (Mohseni-Motlagh et al., 2023).

API and Delivery System	Route of Administration	CQA	CMA
Capecitabine delivery by interpenetrating polymeric network (IPN) microbeads	Oral	-Particle size -Drug entrapment -Drug release	-Amount of polymer -Amount of cross-linker
Posaconazole loaded micellar based in situ gelling systems	Ocular	-Sol-gel temperature -Gelling capacity -Drug content -Log consistency index	-Poloxamer 188 (*w*/*v*%) -Poloxamer 47 (*w*/*v*%)
Apremilast-loaded solid lipid nanocarriers embedded in hydrogel	Topical	-Particle size -EE -PDI	-Lipid content (mg) -Surfactant concentration (%)
Hydrogel containing ketoconazole loaded cubosomes	Topical	-Particle diameter (nm) -PDI -Entrapment efficiency (%)	-Lipid (g) -Surfactant (mg) -Amount of stabilizer in 30 mL (% *w*/*w* of GMO)

Critical Process Parameters (CPPs) can be described as aspects of the manufacturing process that directly affect the final quality of a product. Common CPPs include factors like temperature, stirring speed, sonication time, and homogenization time (Table 3). These factors must be carefully controlled to ensure consistent product quality. Understanding which CMAs influence specific CQAs in a particular drug delivery system can help optimize the manufacturing process by utilizing CPPs and ensure the desired product quality (Mohseni-Motlagh et al., 2023).

Table 3. An example of Critical quality Attributes (CQA) and Critical Process Parameters (CPPs) for hydrogel-based drug delivery system (Mohseni-Motlagh et al., 2023).

API and Delivery System	Route of Administration	CQA	CPP
Solid lipid nanocarriers embedded in hydrogel for topical delivery of apremilast	Topical	-Particle Size -Entrapment efficiency -PDI	-Sonication time
Hydrogel formulation of econazole nitrate-loaded b-cyclodextrin nanosponges	Topical	-Particle size -Entrapment efficiency	-Stirring speed -Homogenization time -Homogenization speed
CS loaded optimized AgN-CA gel (Microwave-assisted)	Topical	-Particle size -Absorbance	-Power of microwave in Watt
Luliconazole-loaded nanostructured lipid carriers (NLCs)	Topical	-Particle size -Entrapment efficiency	-Sonication time
Lidocaine and prilocaine-loaded nanoemulsion system	Topical	-Particle size -PDI	-Homogenization pressure -Homogenization cycle
n-Propyl gallate encapsulated solid lipid nanoparticle-loaded hydrogel for intranasal delivery	Intranasal	-Average hydrodynamic diameter (Z-average) -Polydispersity index (PDI) -Zeta potential	-Temperature at dissolution phase

All API and excipients variables (CMAs and CPPs) are then risk assessed. There are many risk management tools to identify and analyse hazards like qualitative and quantitative approach. researchers often use a risk assessment matrix (RAM) or a risk estimation matrix (REM). These matrices help identify factors that could significantly impact the quality of the final product. The process typically involves Identifying Factors - list all potential factors, such as CMAs and CPPs, that could affect the product's quality. Assessing Impact- each factor is evaluated based on its potential impact on the product's quality. This is often categorized as low, medium, or high impact (Table 4).

Table 4. An example of Initial Risk Assessment Matrix (Mohseni-Motlagh et al., 2023).

CQA	CMA #1	CMA #2	…	CMA #n	CPP #1	CPP #2	…
CQA #1	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High
CQA #2	Low	Medium	High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High
…	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High
CQA #*n*	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High	Low/Medium/High

Sometimes factors with low, medium, and high risk impacts are colored green, yellow, and red, respectively.

Considering Risk Factors - factors are further assessed based on their severity, occurrence, and detectability. Calculating Risk Priority Number (RPN)- The RPN is calculated by multiplying the scores for severity, occurrence, and detectability (Table 5). Prioritizing Factors - factors with higher RPN values are considered higher risk and are prioritized for further investigation. In some cases, statistical methods like regression analysis may be used to identify the most significant factors. However, the specific approach can vary depending on the complexity of the product and the available resources (Mohseni-Motlagh et al., 2023).

Table 5. Risk priority number assessment (Mohseni-Motlagh et al., 2023).

CMA	S (Severity)	O (Occurrence)	D (Detectability)	RPN	Impact on CQA
CMA #1	1-n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
CMA #2	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
…	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
CMA #*n*	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
CPP #1	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
CPP #2	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
…	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m
CPP #*n*	1,2,…,n	1,2,…,n	1,2,…,n	1,2,…,n^3	CQA #*n*, CQA #m

Design of Experiments (DoE) constitutes a cornerstone of the Quality by Design (QbD) paradigm within pharmaceutical development. DoE employs a structured and organized statistical methodology to investigate the correlation between process variables and the resulting product characteristics. It allows for a better understanding of how various input variables affect the output, thus enabling the optimisation of processes. According to sources DoE has largely replaced the traditional 'one factor at a time' (OFAT) approach for drug development and analysis. QbD using DoE offers better results with fewer experimental runs. It is a cost-effective method that describes the main effects of different input variables and their interactions. It also leads to higher yields, reduced development costs, and lower manufacturing expenses (Fiedler et al., 2023). DoE is fundamental in the development of a design space (DS). The design space is defined by the sets of process parameters and material attributes that ensure product quality. Applications for marketing authorisation that include a design space enable

flexible manufacturing operations, so that if deviations in process parameters or material attributes occur, batch rejections or reports to regulatory agencies are not necessary.

Data from DoE is used to create models that describe the relationship between CQAs and CPPs/CMAs through multivariate data analysis. These models are often developed using partial least squares regression (PLS) to achieve a high goodness of fit (Fiedler et al., 2023).

DoE is used to assess the impact of various factors on product quality, which is crucial for risk assessment within the QbD framework (Farooqi et al., 2020). In conclusion, DoE is a powerful statistical tool that is essential to the QbD approach. It facilitates a better understanding of process parameters, helps in optimizing formulations, and ensures consistent product quality while also reducing costs and experimental runs. By using DoE, pharmaceutical companies can develop robust and reliable products while meeting regulatory standards (Zeeshan et al., 2021).

Quality by Design prioritizes knowledge and control throughout the drug development process to guarantee high quality, using sound science and quality risk management (Figure 2).

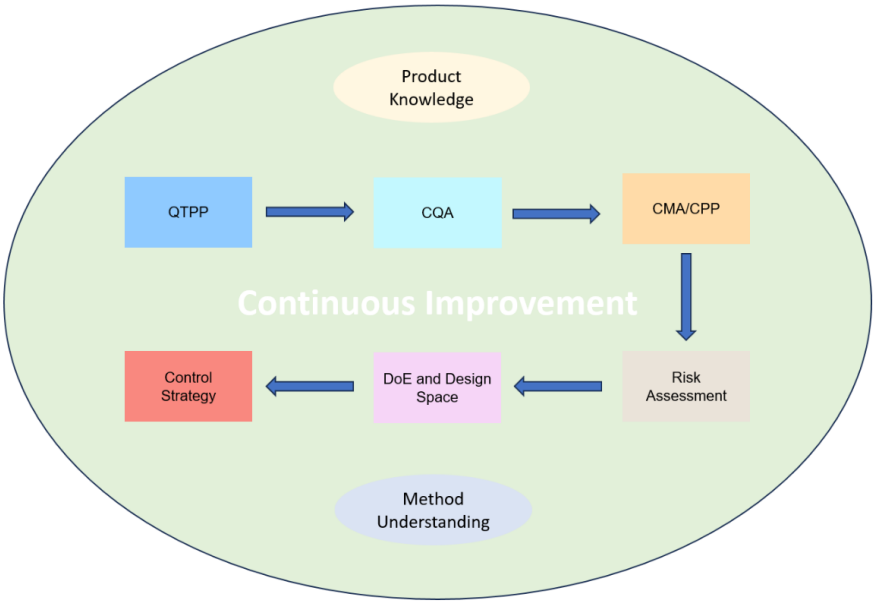

Figure 2. Visual representation of Quality by Design drug development approach.

Certain advantages of QbD are improved product quality and performance, QbD ensures that the finished medicine consistently meets predefined characteristics from the start, building quality into the product from the beginning through a deep understanding of its characteristics and production process. By identifying and controlling critical attributes (CMAs and CPPs) that could impact product quality (CQAs), QbD facilitates achieving the desired quality of the drug products (Zagalo et al., 2022). QbD promotes an enhanced understanding

of the relationship between process parameters and product quality. This understanding leads to more robust and reliable manufacturing processes (Pallagi et al., 2019). The systematic approach of QbD shortens development times and costs, with fewer experimental runs required to assess a variety of factors and identify optimal conditions. It also reduces the likelihood of manufacturing failures and enhances formulation design and performance. QbD leads to a higher success rate in regulatory approvals. By applying QbD principles in regulatory filings, pharmaceutical companies can expect smoother regulatory reviews, fewer manufacturing issues, faster approvals, and a reduced need for post-market manufacturing changes. The establishment of a design space through QbD allows for more flexibility in manufacturing operations without the need for additional regulatory scrutiny, if operations remain within the defined design space. QbD promotes innovation and continuous improvement in the entire product lifecycle. The systematic QbD approach results in high-quality products, with a deep understanding of the product and process, reducing variability and the risk of failure in marketing authorization procedures. The source stats that by 2022 no products developed with a QbD approach have been withdrawn from the market (Zagalo et al., 2022). QbD improves process control and reduces variability, thus reducing off-specification outputs. QbD enhances the ease of technology transfer from lab-scale to large-scale manufacturing (Zagalo et al., 2022).

As per disadvantages of QbD, the implementation can require an initial investment in instrumentation, software, and training, which may be higher than traditional approaches.
QbD can be perceived as a complex approach, requiring more resources for experiments, data collection, and documentation. A successful QbD implementation requires a qualified workforce with expertise in statistical software and multivariate modelling. While QbD is intended to save time in the long run, the initial implementation and planning can be time-consuming. There can be uncertainty about the regulatory benefits of QbD and how regulators will treat QbD submissions. There may be concerns about the level of detail associated with documentation and the hard classification of parameters based on their criticality Applying adequate strategies to handle the large amount of information from QbD can be challenging, as are issues raised by regulatory authorities. There can be uncertainty in design space and concerns related to return on investment when developing the design space. The design space is an optional element of QbD and not mandatory, though highly recommended. This can lead to inconsistent implementation of QbD. Many companies implement only a few QbD elements instead of following all requirements in guidance documents. (Zagalo et al., 2022).

In summary, while QbD offers numerous advantages in terms of product quality, process understanding, and regulatory outcomes, it also presents challenges related to initial costs, complexity, and the need for expertise (Table 6). However, the benefits of QbD are increasingly recognized, leading to wider acceptance and implementation in the pharmaceutical industry.

Table 6. Comparison of advantages and disadvantages of Quality by Desing approach.

Advantages of QbD:	**Disadvantages of QbD:**
Improved product quality and performance	Initial costs and investment
Enhanced process understanding	Complexity of implementation
Reduced development time and costs	Need for expertise
Better regulatory outcomes	Regulatory hurdles
Increased manufacturing flexibility	Lack of full implementation
Continuous improvement	Difficulty with complex products
Reduced risk of market withdrawal	Data challenges
Improved process control and reduced variability	Uncertainty about design space
Facilitated technology transfer	Time consuming
Better understanding of drug product	Not always mandatory

Chapter 3. Comparative Analysis

One of the main challenges in drug development is finding the best way to design and develop drugs that are highly effective and have minimal side effects. This part of the project examines the differences between traditional and Quality by Design (QbD) methods in drug development. It focuses on how these approaches differ in understanding the process, process control, risk management, and regulatory compliance.

3.1 Process Understanding

The traditional approach to drug development primarily relies on demonstrating process reproducibility and testing to meet established acceptance criteria (ICH, Q11 2012). It sets narrow operating ranges for process parameters based on observed data to ensure consistency in manufacturing. This often involves a univariate approach, focusing on one variable at a time (ICH, Q8 2009, ICH, Q11 2012, Farooqi et al., 2020). While the traditional approach can be effective in producing consistent batches, it may provide limited flexibility in responding to variability in materials or processes. This approach often leads to a limited understanding of the complex relationships between process parameters, material attributes, and product quality (Zagalo et al., 2022).

In contrast, Quality by Design (QbD) emphasizes a deep scientific understanding of the product and its manufacturing process (Lu et al., 2024). This approach aims to build quality into the product from the outset, rather than relying solely on end-product testing (Zagalo et al., 2022). The QbD approach involves a more systematic evaluation of the relationships between process parameters, material attributes, and CQAs (ICH, Q8 2009). This often involves the use of multivariate experiments, Design of Experiments (DoE) methodologies, and risk assessment tools to understand the complex interactions within the manufacturing process (Zagalo et al., 2022). The deeper understanding gained through QbD allows for greater flexibility in manufacturing, as well as a more proactive approach to risk management and continual improvement (ICH, Q8 2009, Zagalo et al., 2022).

The use of surrogate materials with similar physical properties to costly proteins can further enhance process understanding in a time- and material-efficient way. The knowledge gained from these experiments can be used to train artificial neural networks (ANNs) to predict CQAs based on material and process factors (Fiedler et al., 2023).

To summarize, the traditional approach to drug development often leads to a limited understanding of the manufacturing process, relying primarily on process consistency and end-product testing. The QbD approach, on the other hand, fosters a deeper scientific understanding of the product and its manufacturing process, allowing for greater flexibility, improved risk management, and a more proactive approach to quality assurance. This is achieved through a systematic evaluation of the relationships between process parameters, material attributes, and CQAs.

3.2 Control Strategy

The traditional approach to drug development typically relies on a control strategy heavily focused on end-product testing and narrow process parameter ranges. This approach aims to assure quality by adhering strictly to established procedures and specifications. While this can produce consistent batches, it offers limited flexibility in responding to variability in raw materials or process parameters (ICH, Q11 2012).

Quality by Design in contrast, leverages a comprehensive understanding of the product and its manufacturing process to develop a more proactive and flexible control strategy (ICH, Q11 2012). This strategy encompasses a range of elements like in-process controls that include monitoring critical process parameters (CPPs) during manufacturing to ensure the process is operating within the defined limits. Controls on material attributes involve setting specifications for raw materials, starting materials, and intermediates to ensure their quality attributes (CMAs) are consistently within acceptable ranges. QbD can facilitate the use of Real-time release testing (RTRT), where the quality of in-process or final product is assessed using process data, potentially reducing the reliance on end-product testing. Finaly, a well-defined design space, encompassing acceptable ranges for CPPs and CMAs, enables flexibility in manufacturing without requiring regulatory post-approval changes if operations remain within the design space (ICH, Q8 2009, ICH, Q11 2012). QbD emphasizes a shift from relying solely on end-product testing to incorporating upstream controls that ensure quality throughout the manufacturing process (ICH, Q11 2012). This is achieved by understanding the relationships between material attributes, process parameters, and CQAs, allowing for informed adjustments and a more adaptable control strategy (Zagalo et al., 2022).

In summary, the traditional control strategy primarily focuses on end-product testing and adherence to rigid specifications, whereas a QbD approach uses process understanding to establish a more proactive and adaptive system. This system involves a combination of in-process controls, material attribute controls, potentially RTRT, and a design space that allows for flexibility and continual improvement throughout the product lifecycle.

3.3 Risk Management

The traditional approach to drug development often involves a reactive approach to risk management, primarily addressing issues as they arise during manufacturing. This approach may rely on end-product testing to identify quality defects and implement corrective actions.

However, it can be less effective in proactively identifying and mitigating potential risks throughout the drug development process.

Quality by Design integrates risk management as a fundamental element, facilitating a proactive and systematic approach such as Failure Mode and Effects Analysis (FMEA), to identifying, assessing, and controlling potential risks to quality. This approach utilizes scientific knowledge and risk assessment tools to understand and manage variability in materials and processes (ICH, Q8 2009, ICH Q9 2023, ICH, Q10 2008, ICH, Q11 2012).

In conclusion, the traditional approach to risk management in drug development is often reactive, relying primarily on end-product testing and limited risk assessment. In contrast, QbD integrates risk management as a core element, employing a proactive, systematic, and science-based approach to identify, assess, and control potential risks. This approach fosters a deeper understanding of the product and manufacturing process, enabling informed decision-making, continuous improvement, and ultimately, the development of high-quality drug (Table 7).

Table 7. A comparison of risk management in traditional and QbD approaches.

Traditional Approach	**Quality by Design (QbD)**
Reactive Risk Management: Addresses quality issues primarily after they occur during manufacturing.	**Proactive Risk Management**: Identifies and assesses potential risks early in the drug development process.
Limited Risk Assessment: May lack a systematic process for identifying and assessing potential risks.	**Systematic Risk Assessment**: Utilizes formal risk assessment tools, such as Failure Mode and Effects Analysis (FMEA), to evaluate potential risks and prioritize mitigation strategies.
Emphasis on End-Product Testing: Relies heavily on testing the final product to detect quality defects.	**Science-Based Risk Control**: Employs scientific knowledge and process understanding to develop effective risk control strategies, encourages ongoing risk assessment and control throughout the product lifecycle to enhance process robustness and product quality.
Limited Process Understanding: May not fully elucidate the relationships between material attributes, process parameters, and quality attributes, hindering proactive risk mitigation.	**Emphasis on Process Understanding**: Focuses on understanding the impact of material attributes and process parameters on quality attributes, enabling proactive risk mitigation.

3.4 Regulatory Compliance

The traditional approach to drug development often involves demonstrating compliance with regulatory requirements through extensive documentation and end-product testing. This approach focuses on meeting pre-defined specifications and adhering to established procedures. However, it can lead to a lengthy approval process with limited flexibility in manufacturing and post-approval changes.

Quality by Design offers a more proactive and science-based approach to regulatory compliance, aiming to build quality into the product from the outset and foster a transparent dialogue with regulatory authorities. This approach utilizes a deep understanding of the product and its manufacturing process to establish a robust control strategy and demonstrate a comprehensive understanding of the risks to product quality. QbD has been increasingly recognized and encouraged by regulatory agencies like the FDA and EMA They promote the use of QbD principles to enhance the quality of pharmaceutical products and streamline the regulatory review process. Submissions that incorporate QbD elements can facilitate a more efficient and science-based assessment by regulatory bodies (Edina Pallagi et al., 2019, Fiedler et al., 2023).

The ICH Q8(R2) emphasizes the importance of QbD elements, such as CQAs, CMAs, and CPPs, in pharmaceutical development. Additionally, the EMA's "Regulatory Science to 2025 Strategic reflection" highlights the role of QbD in addressing scientific and regulatory challenges associated with complex drug products (Huanbutta et al., 2024, Zagalo et al., 2022).

However, despite the advantages of QbD for regulatory compliance, the widespread implementation of this approach faces certain challenges. These include the need for substantial resources, specialized expertise, and a shift in mindset within the pharmaceutical industry. Additionally, regulatory agencies continue to refine their guidance and expectations regarding QbD submissions, requiring ongoing adaptation and collaboration between industry and regulators (Zagalo et al., 2022).

Essentially, the traditional approach to regulatory compliance often involves demonstrating adherence through testing and rigid controls, whereas a QbD approach emphasizes a proactive, science-based approach that fosters a transparent dialogue with regulators. QbD aims to build quality into the product from the outset, providing a comprehensive understanding of the product and its manufacturing process to ensure consistent compliance and facilitate regulatory flexibility. While challenges remain in the full implementation of QbD, its potential to enhance both product quality and regulatory interactions is increasingly recognized and encouraged by regulatory agencies worldwide.

Chapter 4. Impact and Future Trends

The literature sources provide information regarding the impact and future trends of several areas of pharmaceutical development, including Quality by Design (QbD), Artificial Intelligence (AI), and Model-Informed Drug Discovery and Development (MID3).

The impact of Quality by Design (QbD) oh pharmaceutical development was already discussed in previous chapters. additionally, the application of Artificial Neural Networks (ANNs) can be used in conjunction with QbD to develop predictive models for pharmaceutical product development. QbD is being increasingly implemented in the development of complex drug products, such as nanomedicines and non-biological complex drugs (NBCDs) (Huanbutta et al., 2024, Zagalo et al., 2022).

Artificial Intelligence (AI) and Machine Learning (ML) are rapidly transforming a wide range of industries, including the pharmaceutical sector, by enabling advanced data analysis and informed decision-making. Both technologies are being used across various stages of drug discovery and development, including discovering new targets, assessing interactions, and predicting efficacy and safety. ML is being used to enhance the potential of virtual screening (VS) by enabling faster and more precise tracking of forecasted hits. AI facilitates the analysis of large, complex datasets, including multi-omics data, to identify patterns and relationships that can aid in drug discovery. AI and ML are being used in personalized medicine by tailoring treatments to individual patient characteristics, analysing patient-specific data to identify the most effective treatment options (Huanbutta et al., 2024, Majumder & Panigrahi, 2024).

Model-Informed Drug Discovery and Development (MID3) constitutes a comprehensive framework that integrates quantitative models to inform decision-making throughout the drug development lifecycle. This approach utilizes mathematical models of biological, physiological, pathological, and pharmacological processes, underpinned by robust preclinical and clinical data. MID3 aims to enhance the quality, efficiency, and cost-effectiveness of drug development by providing valuable insights at critical decision points. Regulatory agencies, such as the FDA and EMA, recognize the utility of MID3 approaches as valuable decision-making tools to support assessments of efficacy and safety. MID3 is used to estimate the first-in-human (FIH) dose and are expected to be increasingly used in clinical trial design and post-marketing surveillance (Alasmari et al., 2024).

In summary, the pharmaceutical industry is experiencing a significant transformation due to the increasing impact of QbD, AI, ML, and MID3, leading to more efficient, effective, and personalized approaches to drug discovery and development.

Conclusion

The project provides a detailed comparison of traditional and Quality by Design (QbD) approaches to drug development, highlighting the differences in process understanding, control strategies, risk management, and regulatory compliance. The traditional method is characterised by a lengthy and costly process with a focus on end-product testing and reactive risk management. In contrast, QbD is a modern, systematic approach that emphasises a proactive, science-based strategy that aims to build quality into the product from the beginning

Key distinctions between the two approaches are apparent across several domains. The traditional approach often relies on demonstrating process reproducibility and meeting established criteria, with a limited understanding of the complex relationships between process parameters, material attributes, and product quality. QbD, however, emphasises a deep scientific understanding of the product and its manufacturing process, using multivariate experiments and risk assessment tools to analyse these complex relationships.

Traditional methods use a control strategy that relies heavily on end-product testing and narrow process parameter ranges, offering limited flexibility. QbD uses a more proactive strategy, incorporating in-process controls, material attribute controls, and a design space, which allows for greater flexibility and continuous improvement.

The traditional approach is often reactive, addressing issues as they arise during manufacturing. QbD uses a proactive, systematic, and science-based approach to identify, assess, and control potential risks throughout the development process.

The traditional methodology focuses on meeting predefined specifications and adhering to established procedures, which can result in a lengthy approval process with limited flexibility. QbD uses a science-based approach that fosters a transparent dialogue with regulators, demonstrating a comprehensive understanding of the risks to product quality. This often leads to more efficient and science-based assessments by regulatory bodies.

The QbD approach uses several key elements to achieve its goals, including establishing a Quality Target Product Profile (QTPP), identifying Critical Quality Attributes (CQAs), defining Critical Material Attributes (CMAs) and Critical Process Parameters (CPPs), utilizing risk assessment tools, and employing Design of Experiments (DoE). The use of Design of Experiments (DoE) is a key component of QbD, offering a structured method to

understand how various input variables affect the output. This data is used to define a design space, which enables manufacturing flexibility, if operations stay within defined parameters.

While the QbD approach offers numerous advantages, there are some challenges, such as higher initial costs, complexity in implementation, and the need for specialised expertise. Despite these challenges, the benefits of QbD are being increasingly recognised, leading to wider implementation. The project also notes the growing impact of Artificial Intelligence (AI) and Model-Informed Drug Discovery and Development (MID3), which are transforming the pharmaceutical industry by offering advanced techniques for data analysis, decision-making, and the development of predictive models.

In conclusion, the move from a traditional, reactive approach to drug development to a more proactive, science-based approach using QbD, which, along with AI and MID3, is leading to more efficient, effective, and personalised methods in the pharmaceutical industry.

References:

Alasmari, M.S., Albusaysi, S., Elhefnawy, M., Ali, A.M., Altigani, K., Almoslem, M., Alharbi, M., Alghamdi, J. and Alsultan, A. (2024). Model-informed drug discovery and development approaches to inform clinical trial design and regulatory decisions: A primer for the MENA region. *Saudi Pharmaceutical Journal*, 32(12), p.102207.

Duncan, R. "Drug Development and Regulation." *Medicine*, vol. 36, no. 7, July 2008, pp. 369–376.

Edina Pallagi, Orsolya Jójárt-Laczkovich, Zsófia Németh, Piroska Szabó-Révész and Ildikó Csóka (2019). Application of the QbD-based approach in the early development of liposomes for nasal administration. 562, pp.11–22.

Farooqi, S., Yousuf, R.I., Shoaib, M.H., Ahmed, K., Ansar, S. and Husain, T. (2020). Quality by Design (QbD)-Based Numerical and Graphical Optimization Technique for the Development of Osmotic Pump Controlled-Release Metoclopramide HCl Tablets. *Drug Design, Development and Therapy*, Volume 14, pp.5217–5234.

Fiedler, D., Fink, E., Aigner, I., Gerd Leitinger, Keller, W., Roblegg, E. and Khinast, J.G. (2023). A multi-step machine learning approach for accelerating QbD-based process development of protein spray drying. *International journal of pharmaceutics*, 642, pp.123133–123133.

Food and Drug Administration. (2024). *Code of Federal Regulations Title 21*. Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm . [Accessed 16 Nov. 2024].

Grudzinskas, C. (2007). Design of Clinical Development Programs. *Elsevier eBooks*, pp.501–517. [online] Available at: https://doi.org/10.1016/b978-012369417-1/50073-0.

Huanbutta, K. Kanokporn, B. Pakorn, K. Pornsak, S. Thittaporn, G. Kittipat, S. Tanikan, S. (2024). The Artificial Intelligence-Driven Pharmaceutical Industry: A Paradigm Shift in Drug Discovery, Formulation Development, Manufacturing, Quality Control, and Post-Market Surveillance. *European Journal of Pharmaceutical Sciences*, 203, pp.106938.

ICH (2009). International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline *PHARMACEUTICAL DEVELOPMENT Q8(R2)* version 4 [online] Available at: https://database.ich.org/sites/default/files/Q8%28R2%29%20Guideline.pdf.

ICH (2023). International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline *QUALITY RISK MANAGEMENT Q9(R1)* [online] Available at: https://database.ich.org/sites/default/files/ICH_Q9%28R1%29_Guideline_Step4_2023_0126_0.pdf.

ICH (2008). International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline *PHARMACEUTICAL*

QUALITY SYSTEM Q10 version 4 [online] Available at: at: https://database.ich.org/sites/default/files/Q10%20Guideline.pdf.

ICH (2012). International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline *DEVELOPMENT AND MANUFACTURE OF DRUG SUBSTANCES (CHEMICAL ENTITIES AND BIOTECHNOLOGICAL/BIOLOGICAL ENTITIES) Q11)* version 4. [online] Available at: https://database.ich.org/sites/default/files/Q11%20Guideline.pdf.

ICH (1998). International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline *DURATION OF CHRONIC TOXICITY TESTING IN ANIMALS (RODENT AND NON RODENT TOXICITY TESTING) S4* version 4. [online] Available at: https://database.ich.org/sites/default/files/S4_Guideline.pdf.

Ilhan, M. (2022). *What Are the 5 Stages of Drug Development?* [online] Oakwood Labs. Available at: https://oakwoodlabs.com/what-are-the-5-stages-of-drug-development/.

Lu, L., Ni, S., He, X., Huang, Y., Chen, X. and Yang, Z. (2024). From tradition to evidence-base: Leveraging TCM human use experience in modern drug development. *Pharmacological Research - Modern Chinese Medicine*, 13, p.100535.

Majumder, S. and Panigrahi, G.K. (2024). Advancements in Contemporary Pharmacological Innovation: Mechanistic Insights and Emerging Trends in Drug Discovery and Development. *Intelligent Pharmacy*.

Malerba, F. and Orsenigo, L. (2015). The evolution of the pharmaceutical industry. *Business History*, 57(5), pp.664–687.

Medina, A., Dragulin-Otto, S., Cox, E., Fuentes, N., Wang, Y., Flores, K., Lent, I., Glasser, L., Kwok, S.C., Donegan, S., Brown, M.N. and Angeliki Siapkara (2024). Drug Product Development and Case Studies for User Centric Pediatric Protein-Based Therapeutics. *Journal of Pharmaceutical Sciences*.

Mohseni-Motlagh, S.F., Dolatabadi, R., Baniassadi, M. and Baghani, M. (2023). Application of the Quality by Design Concept (QbD) in the Development of Hydrogel-Based Drug Delivery Systems. *Polymers*, 15(22), p.4407

O'Neill, R. O. Y. P. B. L. Y. L., 2024. Edaravone for the Treatment of Motor Neurone Disease: ACritical Review of Approved and Alternative Formulations. *Pharmaceutics*, Volume 16, p. 993.

Pallagi, E. Jójárt-Laczkovich, O. Németh, Z. Szabó-Révész, P. Csóka, I. (2019). Application of the QbD-based approach in the early development of liposomes for nasal administration. 562, pp.11–22.

Pracher, L. and Zeitlinger, M. (2024). Preclinical and clinical studies in the drug development process of European Medicines Agency-approved non-HIV antiviral agents: a narrative review. *Clinical microbiology and infection: the official publication of the European Society of Clinical Microbiology and Infectious Diseases*, [online] pp. 98-743.

Pun, F.W., Ozerov, I.V. and Zhavoronkov, A. (2023). AI-powered therapeutic target discovery. *Trends in Pharmacological Sciences*, 44(9), pp.561–572.

Sudha, S. H. a. T., 2024. QbD- QUALITY BY DESIGN ANALYTICAL METHOD DEVELOPMENT AND VALIDATION-AN OVERVIEW. *Rasayan J. Chem.*, 17(3), pp. 1310-1313.

Van Norman, G.A. (2019). Limitations of Animal Studies for Predicting Toxicity in Clinical Trials. *JACC: Basic to Translational Science*, 4(7), pp.845–854.

Veeranti, V. Fatima, M. and Prasanthi, D. (2023). Quality by Design approach for nanosystem based topical drug delivery. German Journal of Pharmaceuticals and Biomaterials, 2(1), pp.01-17.

Waskiewicz, M.J. (2012). Regulatory guidelines for the development of a biotechnology drug product. pp.115–138.

Zagalo, D.M., Sousa, J. and Sérgio Simões (2022). Quality by design (QbD) approach in marketing authorization procedures of Non-Biological Complex Drugs: A critical evaluation. *European Journal of Pharmaceutics and Biopharmaceutics*, 178, pp.1–24.

Zeeshan, M., Ali, H., Qurat Ul Ain, Mukhtar, M., Gul, R., Sarwar, A. and Khan, S. (2021). A holistic QBD approach to design galactose conjugated PLGA polymer and nanoparticles to catch macrophages during intestinal inflammation. *Materials science & engineering. C, Biomimetic materials, sensors and systems*, 126, pp.112183–112183.