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Figure 1: Quality by Design (QbD) [3]

When applied to API manufacturing the use of QbD implies the identification of a QTPP, the establishment of CQAs and the systematic review of CMAs and CPPs. There is wide use of tools like risk assessment methodologies, DoE Process Analytical Technology (PAT) and multivariate data analysis to develop relationships between process variables and product quality. QbD allows manufacturers to optimize their processes, minimize variability, improve yield, and ensure stable regulatory compliance by creating a design space and employing a successful control strategy.

The optimization of the process by QbD is especially relevant to the production of API in connection with the growing attention of the regulation, the necessity of managing the cost-efficient production, and the complexity of the chemical and biotechnological synthesis pathways [4]. A number of researchers have established that process optimization based on QbD results in better process robustness, fewer batch failures, greater scalability, and lifecycle management, which are more efficient. In addition, QbD supports continuous improvement because it enables manufacturers to implement changes in the post-approval process in an approved design space without substantial regulatory filings.

As much as QbD has been known to have benefits, the adoption of the technique in the manufacture of API is not without problems. It is sometimes prohibited by high start-up cost of experimentation, large data demands and interdisciplinary skills, especially at small-and-medium-scale manufacturing scales. Besides, the differences in regulatory expectations among the regions and the lack of practical guidance of lifecycle QbD implementation make the application more complicated.

Considering the increased role of QbD in the pharmaceutical production process and its potential to revolutionize API process development and optimization, an in-depth and systematic literature review of the current literature is necessary [5]. The proposed review will critically evaluate existing literature on QbD methods to use in process optimization in the manufacturing of API, determine the frequently used tools and strategies, evaluate reported results, and discuss the current challenges and gaps in research. Incorporating existing information, the review aims at offering valuable information to researchers, industry practitioners and regulatory authorities in the development and optimization of high-quality API manufacturing processes.

2. METHODOLOGY OF THE SYSTEMATIC REVIEW

The systematic literature search was employed to find out peer-reviewed studies on the topic of QbD application to optimize the processes in the API manufacturing. Scopus, Web of science and PubMed, science direct and Google scholar were some of the major scientific databases visited to ensure that all published research was covered [6]. The search strategy was based on the combination of the keywords, including, but not limited to, Quality by Design, API manufacturing, process optimization, critical quality attributes, design of experiments, and risk assessment in pharmaceuticals. Articles written in English language within the year 2005 to 2025 were taken into account, as this is the time when QbD became acceptable by the regulation and became applicable to the industry.

Inclusion and exclusion criteria were used to select the studies. Only peer-reviewed journal articles that explicitly used the principles of QbD to the manufacturing of APIs were included and review articles that contained no original analysis, studies that analyzed only finished dosages forms and non-pharmaceutical process studies were excluded [7]. The issues that were extracted in data involved the type of API process used, the QbD tools used, the results of process optimization, and the regulatory relevance. The analyzed data were analyzed through a qualitative synthesis approach that allowed determining common trends,

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methodological strength and limitation, and research gaps in the current literature.

3. FUNDAMENTALS OF QBD IN API MANUFACTURING

QbD is a more formalized and systematic method of pharmaceutical development that focuses on integrating quality into the production process as opposed to focusing on end-product testing. In the case of API manufacturing [8], QbD is initiated by defining the QTPP, which is a description of the desired quality attributes of the API, which are identity, purity, potency, physicochemical characteristics and stability. QTPP is used as the basis of reference and to facilitate the processes of process development and optimization to make sure that the end product, which is API, is continuously aligned with the set requirements of quality and regulatory standards.

According to the QTPP, CQAs are determined. CQAs are quantifiable physical, chemical, biological or microbiological characteristics, which should be kept within given limits to ascertain quality of the products. Assay, impurity level, particle size distribution, polymorphic form and residual solvents are the common CQAs in API manufacturing. All these CQAs are directly affected by both CMAs like purity of raw materials, particle size and moisture content and CPPs like temperature, reaction time, pH, mixing speed, and solvent ratios among various unit operations.

One of the strengths of QbD paradigm is that it provides the development of a clear relationships among CMAs, CPPs, and CQAs based on systematic risk assessment and experimental studies [9]. Process understanding, robustness, and reproducibility can be gained by manufacturers by locating and managing variability in the process. Such knowledge-based solution allows defining a design space, where the parameters of the process can be modified without affecting the quality of the API, thus, creating flexibility in the scaling up and in the routine manufacturing.

In addition, QbD focuses on the use of the effective control strategy, which incorporates the process monitoring, in-process controls, and end-product testing to ensure a reliable quality across the product lifecycle. Monitoring tools which are real time and acceptance criteria which are preset are often used as part of control strategies to ensure that manufacturing process is not going out of the approved design space. The main aspects of the QbD framework and their corresponding functions on the optimization of the API process are summarized in Table 1.

Table 1: Key QbD Elements in API Manufacturing [10]

QbD Element	Description	Role in Process Optimization
Quality Target Product Profile (QTPP)	Desired quality profile of the API	Guides overall process design and objectives
Critical Quality Attributes (CQAs)	Attributes affecting API quality	Ensures compliance with regulatory and quality requirements
Critical Material Attributes (CMAs)	Raw material characteristics	Minimizes variability from input materials
Critical Process Parameters (CPPs)	Process variables impacting CQAs	Enables effective process control and optimization
Control Strategy	Monitoring and control methods	Maintains consistent quality during manufacturing

4. QBD TOOLS AND TECHNIQUES FOR PROCESS OPTIMIZATION

QbD uses a collection of established scientific and statistical instruments to attain an overall process knowledge and successful enhancement in API production [11]. These tools allow systematic identification, assessment and control over factors that condition the quality of products. Among them, the risk assessment methods and DoE are crucial in determining the key variables and setting up the robust conditions of operation, and the developed analytical and data interpretation methods can be used to monitor and improve the processes.

4.1. Risk Assessment Tools

Risk assessment is the foundation of the QbD system as it enables identifying and ranking the variables that can influence CQAs [12]. Risk assessment instruments that are commonly used in manufacturing of API encompass Failure Mode and Effects Analysis (FMEA), Hazard Analysis and Critical Control Points (HACCP) and Ishikawa (Fishbone) diagrams. These are tools that are used systematically in assessing possible failure modes during manufacturing processes, quantifying them, determining their likelihood and severity and a risk priority number is assigned to them to be used in decision making.

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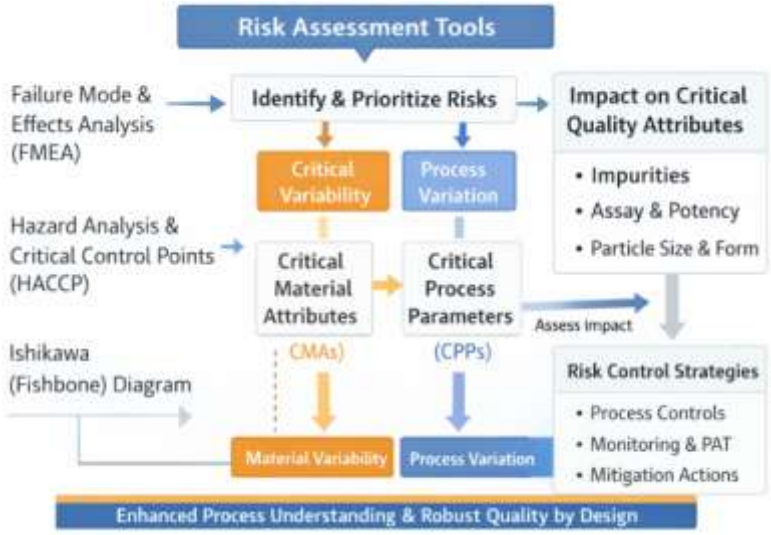


Figure 2: Role of risk assessment tools in QbD for API Manufacturing [13]

Risk assessment is especially applied in the API processes in complex reaction steps, pathways of impurity formation, and scale-up operations. Recent insights into the high-risk CMAs and CPPs allow manufacturers to direct the experimental efforts to variables that need to be controlled to provide the minimal variability and help to minimize the chances of batch failures. The results of risk assessment also contribute to the justification of regulations because they prove the science and risk-based approach to the process development.

4.2. Design of Experiments (DoE)

DoE is a fundamental QbD instrument, which is employed to determine quantitatively the relationships between CPPs and CQAs [14]. DoE as compared to traditional one-factor-at-a-time methods enables the simultaneous analysis of a large number of parameters and interactions, and thus provides a more in-depth insight into process behavior. Specifically, to the API manufacturing process, DoE methods, including full and fractional factorial designs, response surface methodology (RSM) and Box Behnken designs are commonly used to streamline the reaction conditions, solvent mixes, temperature regimens, pH limits and mixing rates.

The use of DoE allows finding out the optimal operating dimensions and contributes to the creation of a design space where it is possible to guarantee a stable quality of API. In addition, DoE leads to higher efficiency in processes through the improvement of yield, lowering the level of impurity and shorter time development schedule. The information produced with the use of DoE is also an excellent scientific foundation of regulations submissions and lifecycle process enhancements.

Besides risk assessment and DoE, other tools that are enabling the application of QbD like Process Analytical Technology (PAT) and multivariate analysis are also being applied more frequently to facilitate real-time monitoring and overall interpretation of data. All these tools help to improve process understanding and promote powerful control strategies. Table 2 gives a summary of usually employed QbD tools in the manufacturing of API and their intended application.

Table 2: Common QbD Tools Applied in API Manufacturing [15]

Tool	Purpose	Typical Application
Failure Mode and Effects Analysis (FMEA)	Risk prioritization	Identification of high-risk reaction steps
Design of Experiments (DoE)	Process optimization	Yield and purity enhancement
Process Analytical Technology (PAT)	Real-time monitoring	Reaction end-point determination
Multivariate Analysis	Data interpretation	Enhanced process understanding and control

5. IMPACT OF QBD ON API PROCESS PERFORMANCE

It has been established that the implementation of the QbD principles has significant positive influence on the performance of the processes in API manufacturing [16]. Various studies indicate that QbD development increases the robustness of the process, boosts yield of the product, improves the control of impurities, and simplifies the process of scaling a development from a laboratory to a commercial production. Through the systematic classification and management of CQAs, CMAs, and CPPs, manufacturers will acquire a better insight into the behavior of processes, which results in the variability being reduced and more predictable manufacturing results. Lee et al. (2022) highlighted that an organized QbD adoption had a great

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impact on the consistency and reproducibility of all the stages of pharmaceutical development, which enhances the performance of the process, in general.

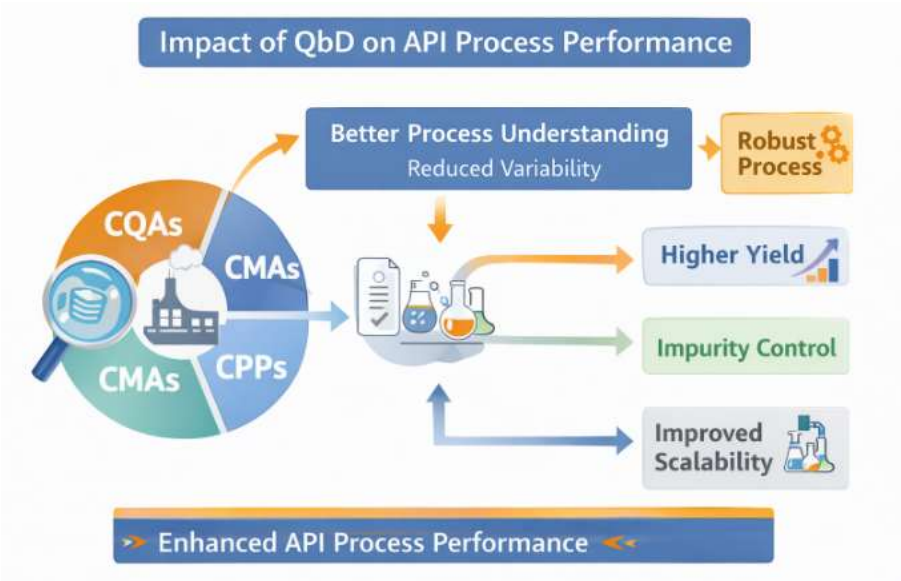


Figure 3: Impact of QbD on API Process Performance [17]

A scientifically justified design space is one of the most important contributions of QbD on API manufacturing. Within an accepted design space, manufacturers can maneuver process parameters at will without sacrificing the quality of API, and it offers increased operational freedom [18]. As mentioned by Mishra et al. (2018), this type of flexibility not only enhances the efficiency of the process but also minimizes the rate of batch failures and deviations. Moreover, according to Duarte et al., QbD-based process optimization facilitates the lifecycle management process through sustaining continuous improvement and facilitating easier transfer of technology and ensuring that the changing regulatory expectations are met (2025).

Implementation of QbD has also been linked to the decrease in post-approval regulatory modifications, since a deep understanding of processes would reduce the number of changes to be conducted. Regulatory authorities are becoming more and more accepting of QbD-based submissions in terms of being scientifically viable, and this aspect may result in quicker approvals and reduced post-marketing obligations. According to recent research, it is also possible to state that the incorporation of QbD and more sophisticated analytical methods and data-driven factors positively affect the impurity profiling, reaction endpoint management, and scale-up consistency. Despite the fact that a good part of the new literature has paid their attention to dosage forms, the results provided by Jeong et al. (2025) support the idea that the principles of QbD-based process optimization are also applicable to upstream API production, especially when it comes to the attainment of the same quality and performance results.

In general, the understanding of QbD application has been uniform across the literature citing that adoption of the QbD results in significant change in API process performance, regulatory confidence and manufacturing efficiency. Table 3 provides a comparative summary of the representative studies that report the effects of QbD on the performance of processes with major findings in various pharmaceutical settings.

Table 3: Impact of QbD on Pharmaceutical Process Performance – Key Studies

Author(s)	Year	Focus Area	Key QbD Impact Reported
Lee et al. [19]	2022	Pharmaceutical development processes	Improved process robustness and reproducibility
Mishra et al. [20]	2018	Pharmaceutical manufacturing systems	Enhanced yield, reduced variability, regulatory flexibility
Duarte et al. [21]	2025	R&D, manufacturing, and quality assurance	Lifecycle optimization and improved regulatory compliance
Jeong et al. [22]	2025	Process optimization and quality enhancement	Better impurity control and process consistency

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6. CHALLENGES

Although the positive effect of QbD on the ability to understand processes better and improve the performance of manufacturing processes has been well-documented, its application to the manufacturing of API faces various technical, organizational, and economic issues. Among the main impediments is the fact that high initial investment is needed to conduct extensive experimentation, generate data systematically and implement advanced tools of analysis [23]. The successful application of DoE, Process Analytical Technology (PAT), and multivariate data analysis is expensive in financial and infrastructural terms and may be especially difficult to implement in the small-scale pharmaceutical producer when process development is in its initial phases.

The necessity of the multidisciplinary competence and cross-functional cooperation is another crucial issue [24]. Effective QbD implementation is based on the efforts of chemists, chemical engineers, statisticians, quality assurance professionals and regulatory experts working as a team. Nevertheless, the lack of talented staff and the training of sophisticated statistical and risk-based techniques can usually limit the richness and regularity of QbD implementation. Moreover, the organizational opposition to the change is also a major challenge, and the transition to the proactive and knowledge-based quality framework cannot be achieved without cultural change, process redirection, and the leadership dedication.

In addition, management and interpretation of big and complicated datasets obtained in the course of QbD studies contribute to the complexity of implementation. The manufacturing processes of API produce lot of experimental, analytical and real time monitoring information that is hard to integrate, analyze and maintain without strong digital infrastructure. The absence of a unified data management system and minimal integration of the development and manufacturing platforms also makes the decisions more complicated [25]. These issues will require long-term management assistance, special training programs, and planned investment in digital technologies like PAT, progressive analytics, and complex data management systems. The successful implementation of the tools is the key to reaping the most out of the long-term benefits and sustainability of QbD-driven manufacturing of API.

7. CONCLUSION

This systematic review exemplifies QbD as a solid and efficient tool of process optimization in the production of API. QbD provides a systematic control of CQAs by incorporating scientific knowledge, risk-based evaluation, and data-driven experimentation by controlling the CMAs and CPPs systematically. All of the reviewed literature shows that the implementation of QbD results in improved process strength, increased yield, improved control over impurities, scalable manufacturing, and increased regulatory confidence due to the creation of a scientifically rational space of design. Despite the issues associated with the implementation price, data complexity, and multidisciplinary skills, further development of process analysis technology and digital tools as well as sophisticated analytics should streamline its wider use. In general, QbD is a revolutionary method of attaining sustainable, high-quality, and efficient manufacturing of API to promote continual improvement and regulatory flexibility throughout the product lifecycle.

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