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Touchless Quality Control in Pharma Using a Digital Twin–Driven Fuzzy Multi-Objective Optimization Framework for Risk-Aware Release Decisions

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Abstract
Quality control in the pharmaceutical industry has always faced a fundamental challenge in balancing product release speed, safety, operational costs, and regulatory requirements. In many pharmaceutical organizations, the final decision for batch release still relies on extensive human reviews and conservative procedures, which leads to operational bottlenecks and reduced organizational agility. Despite recent advances in digital twin and risk-based approaches, a unified and operational framework for realizing quality control without direct human intervention has not been systematically developed. This research presents, for the first time, a closed-loop framework for touchless quality control (Touchless QC) based on the integration of hybrid digital twin, fuzzy multi-objective optimization model, and human intervention mechanism under exceptional conditions. In this framework, the digital twin of the laboratory flow simulates the propagation of quality risk and resource constraints, and the multi-objective optimization engine simultaneously minimizes the release time, cumulative quality risk, quality control costs, human intervention rate, and laboratory congestion under GMP and SLA constraints. The meta-heuristic algorithms NSGA-II, MOEA/D, and MOPSO are used to extract the Pareto front. Results from real and simulated industrial data show that the proposed framework is able to significantly reduce the release time and quality control costs, while maintaining the quality risk level at an acceptable level or even lower than traditional policies. Also, release decisions are made in a structured and automated manner, and human intervention is activated only when risk or uncertainty thresholds exceeds the defined limits. In addition to improving operational performance, this framework also enhances transparency, traceability, and regulatory robustness of decisions, and is a practical step towards realizing smart, risk-based quality control in the pharmaceutical industry.

Keywords- Non-contact quality control, Digital twin, Risk-based decision making, Batch release, Fuzzy multi-objective optimization.

1. Introduction

In recent decades, the pharmaceutical industry has faced increasing pressure to balance speed, safety, and compliance with regulatory requirements. Increasing complexity of manufacturing processes, product diversity, shorter drug lifecycles, and greater sensitivity to quality risks have made quality control a major bottleneck in the industry's operational and competitive performance (Lu et al., 2025). In many pharmaceutical organizations, batch release decisions are still largely based on manual procedures, human reviews, and conservative policies; policies that, while designed to ensure safety, in practice lead to unnecessary delays, high resource consumption, and reduced organizational agility. These challenges are particularly acute in environments where stringent regulatory requirements are coupled with variable process and laboratory data (Priya et al., 2025).

In response to these conditions, the concept of "contactless quality control" has been proposed as a new approach that aims to reduce the dependence on human intervention and move towards data- and risk-based decision-making. However, the practical implementation of such an approach is accompanied by serious obstacles (Cao, 2025). On the one hand, completely eliminating human oversight is not only unacceptable from a regulatory perspective, but it can also lead to hidden risks and unforeseen consequence. On the other hand, the mere use of static analytical tools or simple decision-making rules cannot represent the complex dynamics of quality control systems. In the meantime, digital twin, as an enabling technology, has the potential to bridge the gap between real data, system behavior, and management decision-making (Maculotti et al., 2025).

By providing a dynamic and updatable picture of processes, the digital twin allows the behavior of the quality control system to be simulated and predicted, beyond mere observation. However, the use of the digital twin alone is not sufficient to solve the release decision-making problem, because quality control decisions are inherently multi-objective and must balance conflicting goals such as reducing release time, minimizing quality risk, controlling costs, and meeting compliance requirements. This feature highlights the need for multi-objective optimization frameworks (Cai et al., 2025). Furthermore, the uncertain nature of laboratory and process data requires that risk assessments and decision-makers' preferences be modeled in a fuzzy and flexible manner (Barykin et al., 2020).

The main innovation of this research lies in presenting an integrated framework that, for the first time, brings the concept of non-contact quality control to the level of implementation and practical application by combining digital twin, fuzzy multi-objective optimization, and exception-based human-in-the-loop mechanism. Unlike existing approaches that either emphasize complete automation or still rely on extensive human intervention, the proposed framework attempts to strike a smart balance between automation and human supervision. In this framework, release decisions are generated by default by the optimization engine based on predictive analytics from the digital twin, and human intervention is activated only when the level of risk or uncertainty exceeds defined thresholds. This approach is in line with the logic of risk-based regulation. It also allows human resources to be focused only on truly critical cases (Arulmozhi et al., 2024).

From a methodological perspective, this research provides a flexible and scalable framework that can cover various operational scenarios by developing a fuzzy multi-objective mathematical model and solving it using advanced meta-heuristic algorithms. Validation of the results through comparison with the exact solution in reference environments, along with the simultaneous use of real and simulated data, strengthens the confidence in the reliability of the results. In addition, stability analysis, sensitivity analysis, and comparison with traditional quality control policies show that the proposed approach is not only superior in terms of optimality, but also has significant advantages in terms of decision stability and applicability in industrial environments.

Accordingly, this research takes a step beyond previous studies and elevates non-contact quality control from a theoretical concept to a practical and defensible framework for decision making. The importance of this work is not only limited to improving operational performance, but also in creating transparency, traceability and defensible decisions in regulatory environments; Features that are absolutely critical for industrial and regulatory acceptance of such approaches.

The structure of the paper is arranged in such a way that at the beginning, the research problem and questions are explained in the context of pharmaceutical quality control. Then the proposed framework and its architecture are described and the role of the digital twin in modeling and simulation of the quality control system is examined. Next, mathematical modeling and solution methods are presented and the

results of various analyses are reported and interpreted. Finally, managerial implications and a final conclusion of the research are presented.

2. Literature Review

Quality control in the pharmaceutical industry has always been one of the most sensitive and complex parts of the production chain; a part that is directly linked to patient safety, regulatory compliance, and organizational credibility. Previous studies show that traditional quality control approaches have relied mainly on end-of-process testing, extensive human reviews, and conservative release policies (Cesur et al., 2025). Although these approaches have played an important role in quality assurance in the past decades, with the increasing complexity of pharmaceutical products, the continuous growth of process data, and the increasing pressure to reduce product time to market, their inefficiencies are now more apparent than ever (Jiang & Wang, 2025).

In recent years, attention has shifted from reactive quality control to predictive and risk-based approaches. In this regard, concepts such as real-time quality control and data-driven liberalization have been proposed as solutions to reduce latency and increase transparency in decision-making (Doerr et al., 2025). However, a significant part of these studies is still based on static frameworks or simple decision-making rules; frameworks that are unable to accurately represent the complex dynamics of real quality control systems. In addition, the role of uncertainty in laboratory and process data is either implicitly considered or oversimplified in many of these approaches (Zhang et al., 2022).

Meanwhile, digital twin, as an emerging technology, has attracted great attention in various industrial fields. A number of studies have shown that digital twins can provide a dynamic picture of physical systems, enabling monitoring, prediction, and analysis of different scenarios (Han et al., 2025). In the pharmaceutical industry, digital twin applications have focused more on modeling manufacturing processes and optimizing operating parameters, but sometimes it not fully considers all practical constraints. However, the use of this technology specifically to support quality control and batch release decisions is still in its infancy and in many cases is limited to descriptive analyses or simulations (Huang et al., 2021).

On the other hand, quality control decisions are inherently multi-objective and require balancing conflicting goals such as reducing release time, minimizing quality risk, controlling costs, and meeting regulatory requirements. The multi-objective optimization literature shows that the use of single-objective algorithms or methods based on fixed weights cannot fully reflect these complex trade-offs (Mo et al., 2023). For this reason, evolutionary multi-objective optimization algorithms have been widely used in various engineering and management problems. However, their application to pharmaceutical quality control problems is often limited to issues such as laboratory scheduling or resource allocation, and rarely considers the final release decision in a comprehensive framework (Ren et al., 2025).

Another important weakness in the existing literature is how to deal with uncertainty and human judgment. Many studies assume that input data are accurate and error-free, while in practice, test results, process conditions, and even the perceptions and interpretations of quality assurance experts are all subject to some degree of uncertainty (Kim et al., 2023). The use of fuzzy logic as a tool to model these uncertainties has been proposed in some studies, but these approaches have often been used independently and without being linked to a comprehensive decision-making framework (Oliveira et al., 2024).

The role of humans in the decision-making loop is also a controversial topic in the quality control literature. Some studies emphasize the maximum elimination of human intervention and the move towards complete automation (Zhang et al., 2025), while other studies show that the complete elimination of human

supervision is not only challenging from a regulatory perspective, but can also create new risks (Ding et al., 2025). What has received less attention in the literature is the design of an intelligent mechanism for purposeful integration of humans into the decision-making loop, such that human intervention is activated only in exceptional and high-risk situations (Melesse et al., 2022).

A review of existing studies shows that although each of the digital twin components, multi-objective optimization and fuzzy logic, has been investigated separately in related fields, an integrated framework that simultaneously applies these elements to non-contact quality control in the pharmaceutical industry has not yet been systematically addressed (Sepahi-Boroujeni & Khameneifar, 2024). In particular, the lack of a model that can support release decisions in a predictive, risk-based, traceable and compliant with regulatory requirements can be identified as a serious research gap (Wang et al., 2024).

Although numerous studies have investigated the application of digital twin, multi-objective optimization, and fuzzy logic in various manufacturing domains, most of them have focused on process modeling, predictive maintenance, or resource scheduling. From this perspective, the present framework has similarities with these works in using advanced analytical tools and a data-driven approach. However, the fundamental difference of the present study can be observed in several aspects. First, previous studies have not mainly investigated the batch release decision in pharmaceutical quality control as a closed-loop multi-objective problem. Second, the simultaneous integration of digital twin with fuzzy multi-objective optimization in a framework compatible with GMP constraints and an exceptional human-in-the-loop activation mechanism has not been reported in the literature. Third, many previous studies have lacked an implementation mechanism to produce an implementable and regulatory-defensible operational policy. Therefore, the innovation of this research lies not in the isolated application of existing tools, but in their structured, operational, and scalable integration into a decision-support architecture for non-contact quality control.

Accordingly, the main gap in the literature can be considered the lack of a comprehensive framework that can simultaneously and coherently model the dynamics of the quality control system, data uncertainty, multi-objective trade-offs, and the human role. Focusing on this gap, the present study attempts to provide an innovative approach that takes non-contact quality control beyond the level of conceptual ideas and turns it into a practical decision-support system that can be used in real pharmaceutical environments.

3. Problem Definition and Research Questions

In pharmaceutical quality control, the issue is not limited to performing a set of tests. The main issue is to make a reliable release decision in a situation where data is not always complete, not free of noise, and not necessarily available at the same time; at the same time, each decision must be defensible from the perspective of adaptability and auditability. The focus of this research is on a common scenario in many pharmaceutical factories, namely batch release, where the final result must balance delivery speed, laboratory costs, resource constraints, and quality risks. However, the proposed framework is designed in such a way that it can be extended to two other important applications: laboratory scheduling and near-real-time decision-making to reduce release delays (Real-time/near-real-time release support). In all three applications, the common point is the need for a closed decision loop that can adjust the quality control program to changes, measurement errors, and unforeseen events, with minimal manual intervention.

This problem is inherently multi-objective. On the one hand, Time-to-Release should be reduced as much as possible, as it is an indicator that directly affects serviceability, revenue, and market satisfaction. On the other hand, the cost of quality control is not limited to consumables and kits, but also includes operator time, equipment occupancy, test repetitions, queue delays, and costs resulting from conservative decisions.

In addition, quality risk should be managed systematically, as even a small reduction in the probability of OOS/OOT events or the prevention of risky releases has a very high operational and compliance value. Another goal is to maintain compliance and auditability; meaning that the proposed decision should not simply be "better," but the path taken and the decision logic should also be reproducible and documented for the QA team and external auditor. Finally, the pressure on laboratory resources and operational sustainability are also essential criteria, because in practice any policy that seems optimal on paper will not be successful in implementation if it leads to increased congestion and fragility of the laboratory program.

In such a framework, decision variables are the tools through which the Touchless system can not only "measure" quality, but also "plan" for it. In this study, policy decisions are modeled, including determining the frequency and timing of sampling and under what circumstances sampling should be intensified or reduced; prioritizing tests and adjusting their sequence in such a way as to both improve release time and reduce the risk of ignoring warning signs; allocating resources including equipment, shift capacity, and manpower to control laboratory queues and prevent bottlenecks; Determining the level of human review that determines which decisions can be made without manual intervention and which ones should be referred to the QA team; and finally defining exception thresholds that move the system from a "no-touch" state to a "human-in-the-loop" state, such as unstable patterns in the data, increasing measurement uncertainty, or early signs of OOT that have not yet become OOS. This set of decisions is deliberately chosen so that their output is direct and actionable; in other words, the system does not just provide an overall score or general recommendation, but rather provides a specific policy for action.

Despite this scope of discretion, pharmaceutical quality control is subject to strict constraints, and any decision support framework that does not realistically consider these constraints will soon become unusable. Equipment and shift capacities are limited, and setup, calibration, and maintenance times do not allow for simplistic planning. GMP minimums and internal QA policies also typically set hard boundaries; for example, minimum number of tests, requirement for repeatability under specified conditions, or need for final confirmation at certain decision points. OOS/OOT rules and procedures also impose important practical constraints, as managing out-of-specification or out-of-process events is not just a laboratory result, but a process that involves investigation, documentation, and decision-making, consuming time and resources. In addition, expected service levels (SLAs) also impose clear time and operational constraints on the timely delivery of results and batch release. Hence, the problem of this research is defined as a multi-objective decision-making problem under conditions that face both strict constraints and significant uncertainties. In such a context, fuzzification plays a fundamental role, as it allows soft boundaries, expert judgments, and measurement uncertainties to be introduced into the model without reducing the problem to a set of unrealistic and completely deterministic assumptions.

Accordingly, the research questions are formulated to both address the theoretical value of the framework and provide measurable results in a real-world environment. The first question is whether the integration of Digital Twin with fuzzy multi-objective optimization can significantly improve risk-based release decisions, such that both release time is reduced and quality risk is controlled. The second question concerns "touchless" behavior and raises the issue of under what conditions the share of automated decisions can be increased without compromising adaptability or auditability; and how exception thresholds should be set to both prevent costly errors and minimize human intervention to a reasonable extent. The third question is dedicated to operational efficiency and examines whether the proposed framework can make the load on laboratory resources more stable and reduce bottlenecks, while maintaining service level agreements (SLAs) and QA requirements. The fourth question focuses on robustness and measures the extent to which the generated policies remain stable and whether the resulting Pareto front still provides reliable options in the event of increasing measurement uncertainty, data noise, or input fluctuations. Finally, the fifth question

focuses on the feasibility of implementation and asks whether the model output can be translated into deployable and auditable policies in the QC process, acceptable to both technical and compliance teams.

The hypotheses of this study are also formulated based on these questions. The first hypothesis states that the proposed framework can significantly reduce release time compared to conventional manual scheduling methods or fixed rules without increasing quality risk, and this improvement is achieved through what-if simulation in the Digital Twin and risk-based selection in the Pareto space. The second hypothesis states that the use of fuzzification to model uncertainty and soft constraints produces more stable and realistic decisions than deterministic models and performs better in the face of noise and operational changes. The third hypothesis claims that an exception-based mechanism can increase the proportion of automated decisions while maintaining a level of adaptability and auditability, activating human intervention only when risk or uncertainty indicators cross a certain threshold. The fourth hypothesis also emphasizes that the proposed framework can reduce laboratory congestion and program fragility by simultaneously optimizing resource metrics, thereby improving operational sustainability along with release speed. These hypotheses will be directly tested with measurable metrics in the empirical part and case study to move the research result beyond the level of conceptual idea and into defensible operational evidence.

4. Proposed Framework Overview

The proposed framework in this study is designed to support risk-based release decisions in pharmaceutical quality control and realizes the concept of "Touchless QC" by integrating digital twin and fuzzy multi-objective optimization in a closed-loop architecture. As shown in **Figure 1**, this framework consists of several interconnected layers that operate sequentially and at the same time feedback, covering the decision-making flow from raw data to decision implementation and outcome monitoring.

At the base of this architecture is the data layer, which is responsible for integrating and preparing various sources of quality-related information. These sources usually include the results of quality control tests recorded in LIMS systems, data from laboratory activities, deviation records and previous reviews, as well as the rules and expertise of QA teams. If available, process data can also be fed into the system to enrich the analysis. This layer does not simply serve the role of data transfer, but rather provides the necessary platform for traceable and auditable decision-making by temporal and structural alignment of data.

The processed data is then transferred to the quality control digital twin. In this framework, the digital twin acts as a virtual representation of the actual quality control flow and is able to simulate the behavior of the system under different scenarios. This capability allows for the execution of "what if" analyses; in such a way that the effect of changing sampling policies, test prioritization, or laboratory resource constraints is evaluated before implementation in the real environment. The output of the digital twin includes predictions of indicators such as release time, quality control costs, quality risk level, and operational resource load, which are the basis for decision-making in subsequent stages.

In order to account for the inherent uncertainties in the data and quality judgments, the digital twin output is fed into a fuzzy modeling layer. In this layer, concepts such as risk level, confidence in measurement results, and operational acceptance limits are represented as fuzzy membership functions. Also, some of the requirements and constraints that are not deterministic in nature (such as flexibility in release time or boundary interpretation of OOT results) are modeled as fuzzy soft constraints. This approach allows for a realistic representation of operational conditions without oversimplification.

The decision-making core of this framework is a fuzzy multi-objective optimization engine that simultaneously considers conflicting goals. These goals typically include reducing release time, reducing

quality control costs, minimizing quality risk, maintaining compliance with regulatory requirements, and controlling the burden on laboratory resources. Rather than providing a single solution, the engine produces a set of Pareto solutions that represent possible trade-offs among these goals. As shown in **Figure 1**, this process is guided by explicit constraints such as GMP minimums, equipment and shift capacities, OOS/OOT management procedures, and service level agreements (SLAs).

Since Pareto solutions alone are not feasible, the framework also includes a release decision policy layer that translates the optimization results into operational actions. This layer selects or prioritizes a specific action based on risk-based preferences and quality assurance rules; actions such as batch release, temporary halt, test rerun, or initiating a deviation review process. The decision logic at this stage is designed to ensure that speed of decision-making is not sacrificed at the expense of safety and adaptability.

The selected decision is implemented through a hands-off execution mechanism and an exception gate. Under steady-state conditions, when risk and uncertainty indicators are within defined limits, decisions are executed automatically and human intervention are eliminated. However, if any of the indicators cross defined thresholds, such as a sudden increase in uncertainty, near-OOT patterns, or conflicting test results, the system automatically enters Human-in-the-Loop mode and the decision is referred to a human expert for review. This mechanism provides a balance between operational efficiency and regulatory control.

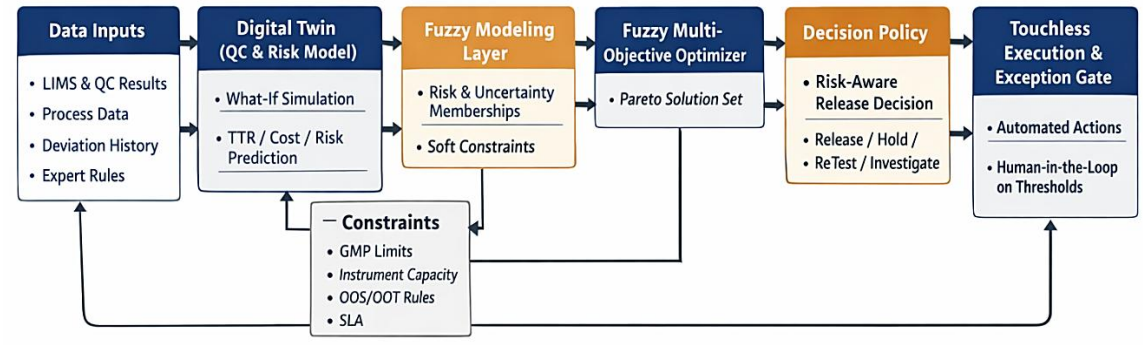

Figure 1. Non-interventional quality control framework with digital twin and fuzzy multi-objective optimization.

The entire framework operates as a closed loop, but it not always perfectly synchronized. The results of decision execution and performance indicators are continuously monitored and fed back to the data layer to provide a basis for updating the digital twin and adjusting decision policies in subsequent iterations. This feature transforms the framework from a static tool to an adaptive decision support system.

From an operational output perspective, the proposed framework produces three main and integrated outputs. First, a clear and actionable operational recommendation is provided that directly leads to a specific quality control action. Second, each recommendation is provided with a risk profile or confidence level that explicitly expresses the degree of decision uncertainty. Third, all decision-making steps, from input data and simulated scenarios to optimization results and decision selection logic, are automatically recorded in an audit trail. This decision-making footprint ensures transparency, traceability, and defensible decisions in quality assurance processes as well as in internal and external audits.

The framework presented in this research has the potential to be used in several practical scenarios in the pharmaceutical industry. First, in the batch release process, this model can act as a decision support system

to determine the optimal testing policy, resource scheduling, and human intervention activation, reducing release time without increasing risk. Second, in laboratory scheduling, the proposed framework can help optimize the allocation of equipment and operators under capacity constraints and prevent the formation of chronic bottlenecks. Third, in environments with stringent regulatory requirements, this model facilitates regulatory defense and internal and external audits by creating a traceable decision path and fully documenting the optimization process. Fourth, in near-Real-Time Release scenarios, the proposed framework can support predictive decision-making and help reduce operational delays by integrating process and laboratory data. Hence, this technique is not just an analytical tool, but an operational architecture for intelligent quality control management in real industrial environments.

5. Digital Twin for Quality Control

In this study, the digital twin is defined as the analytical and predictive core of a non-interventional quality control framework. Unlike some common applications of the digital twin that focus only on the representation of the manufacturing process, the twin used in this study is defined as a hybrid twin that covers both the quality control flow and its relationship with process data. In other words, this twin is not simply a "QC flow twin" that simulates the operational behavior of laboratory activities and quality assurance decisions, but if appropriate data are available, it can also act as a "process-quality control twin" that considers the interaction between process variables and quality outcomes. This hybrid definition allows the consequences of control decisions on the final product quality to be analyzed in a more comprehensive way, although it not fully capturing every possible interaction.

The modeling of the quality control flow in the digital twin is based on an accurate representation of the actual QC steps. The flow begins with the sampling process, where sampling timing, frequency, and policies are modeled as configurable parameters. Samples then enter the laboratory queue, where equipment capacity constraints, operator availability, and shift scheduling affect wait times. Each laboratory test is modeled with its own execution time and the likelihood of repeat testing, so that events such as borderline results, measurement errors, or OOS/OOT conditions are realistically reproduced. After the tests are completed, the review and approval phase by the quality assurance (QA) unit is also included as a potential bottleneck in the model, a phase that is often affected by workload, case complexity, and internal organizational policies. This end-to-end modeling allows the digital twin to represent the dynamic behavior of the QC system not as a static queue, but as a dynamic system of decision-making and queuing.

In the digital twin implementation, the laboratory flow is modeled as a discrete-event system in which each sample is placed in a queue based on the capacity of the equipment and operators upon arrival. Equipment and human resources are allocated according to capacity constraints and shift schedules, and the waiting time for each test is a function of the queue status and the current laboratory load. Test repetition is modeled as a probabilistic mechanism dependent on the batch risk level; in such a way that if the results are in the borderline area or the uncertainty index increases, the probability of activating a retest increase. The quality assurance (QA) unit review stage is also included in the model as an independent decision node with variable processing time dependent on the complexity level of the case. If the risk and threat index or uncertainty exceeds defined thresholds, the case is sent to a human review path and the delay caused by this step is factored into the final release time. This structure allows the interaction between the lab queue, test iterations, and QA review to be dynamically simulated under different operational conditions.

In addition to representing the operational flow, the digital twin also includes a quality risk model that plays a key role in risk-based decision-making. This risk model is based on laboratory data and, if available, process data and reflects the relationship between key process variables (CPP) and critical quality attributes (CQA). In this way, changes in process conditions or patterns observed in test results can increase or

decrease the level of quality risk. The risk model is designed to consider not only obvious events, such as OOS, but also weaker and more gradual signals, such as trends approaching OOT or increasing variance of results. This approach allows for early identification of increased risk and proactive response, avoiding purely reactive decision-making.

A central capability of the digital twin in this framework is the presence of a scenario and simulation module, which acts as a "what-if" analysis engine. This module allows for the simultaneous examination of multiple decision-making scenarios; for example, the impact of a change in test prioritization policy, an increase or decrease in sampling frequency, a sudden limitation of laboratory resources, or a delay in a key test can be simulated on release time, cost, and quality risk. The output of these simulations is presented in a quantitative and comparable form and forms the direct input to the fuzzy multi-objective optimization engine. In this way, decision-making is not based on single guesses or mere experience, but on a systematic analysis of possible scenarios.

To ensure the reliability of the digital twin, the validation process and its reliability measurement are considered as an integral part of the proposed framework. The validation in this research is based on three main axes. First, the structural and behavioral compatibility of the twin with the reference data or scenarios is examined to ensure that the logic of the QC flow and time dependencies are correctly represented. Second, the twin's prediction error in estimating indicators such as release time or the load on laboratory resources is evaluated and the extent of its deviation from the reference values is analyzed. Third, a sensitivity analysis is performed to determine how changes in key parameters, such as test time, repeatability or risk thresholds, affect the twin's outputs. This analysis not only helps to measure the robustness of the model, but also provides valuable insight into the dominant factors in the performance of the QC system.

6. Fuzzy Multi-Objective Optimization Model

Quality control in the pharmaceutical industry is inherently a multi-objective, dynamic, and uncertainty-based decision-making problem in which operational objectives, quality risks, and regulatory requirements must be satisfied simultaneously. In such an environment, reliance on single-objective decision-making or fixed rules cannot account for the real complexity of the system. On the one hand, reducing release time and quality control costs is of great economic importance, and on the other hand, any increase in quality risk or violation of GMP requirements can have irreparable consequences. In addition, the limitations of laboratory resources, the uncertainty of measurement results, and the need for human intervention in certain situations turn decision-making into a problem with a nonlinear and multilayered structure.

For this reason, in this study, quality control is formulated as a fuzzy multi-objective optimization problem in which decisions related to sampling policy, test scheduling and prioritization, resource allocation, and the level of human intervention are determined simultaneously. The digital twin acts as a data generator and decision outcome estimator, while the mathematical model provides a formal framework for finding a set of Pareto-optimal decisions under hard and soft constraints, but sometimes it not capture all interactions exactly. In the following, the components of this model are systematically introduced.

***Sets*:**

$i \in I$: set of production batches

$j \in J$: set of quality control tests

$k \in K$: set of laboratory instruments

$l \in L$: set of QC operators/analysts

$t \in T$: set of time periods or shifts
$s \in S$: set of uncertainty scenarios generated by the digital twin
$r \in R$: set of quality risk types (e.g., OOS, OOT, deviations)

***Parameters*:**
p_{ij} : processing time of test j for batch i
c_{ij} : cost of performing test j for batch i
cap_{kt} : capacity of instrument k in period t
cap_{lt} : capacity of operator l in period t
α_{ij} : probability of re-testing for test j and batch i
β_{ir} : severity of quality risk r for batch i
γ_j : criticality weight of test j
SLA_i : maximum allowable release time for batch i
GMP_j : GMP requirement indicator for test j
θ_r : acceptance threshold for quality risk type r
M : sufficiently large constant (Big-M)

***Decision Variables*:**
$x_{ijt} \in \{0,1\}$: 1 if test j for batch i is performed in period t
$y_{ijt} \in \{0,1\}$: 1 if test j for batch i is repeated
$z_{ikt} \in \{0,1\}$: 1 if instrument k is assigned to batch i at time t
$w_{ilt} \in \{0,1\}$: 1 if operator l is assigned to batch i at time t
$h_i \in \{0,1\}$: 1 if human intervention is required for batch i
$R_i \geq 0$: aggregated quality risk level of batch i
$T_i \geq 0$: total release time of batch i

***Objective Functions*:**

$$\min f_1 = \sum_{i \in I} T_i \tag{1}$$

$$\min f_2 = \sum_{i \in I} \sum_{j \in J} \sum_{t \in T} c_{ij} x_{ijt} \tag{2}$$

$$\min f_3 = \sum_{i \in I} R_i \tag{3}$$

$$\min f_4 = \sum_{i \in I} h_i \tag{4}$$

$$\min f_5 = \sum_{k \in K} \sum_{t \in T} \left(\sum_{i,j} z_{ikt} - cap_{kt} \right)^2 \tag{5}$$

***Constrains*:**

$$\sum_{t \in T} x_{ijt} \leq 1 \; \forall i, j \tag{6}$$

$$x_{ijt} \geq GMP_j \; \forall i, j \tag{7}$$

$$y_{ijt} \leq x_{ijt} \; \forall i, j, t \tag{8}$$

$$y_{ijt} \geq \alpha_{ij} \cdot R_i \tag{9}$$

$$\sum_{k\in K} z_{ikt} = x_{ijt} \; \forall i,j,t \tag{10}$$

$$\sum_{i,j} p_{ij} z_{ikt} \leq cap_{kt} \; \forall k,t \tag{11}$$

$$\sum_{l\in L} w_{ilt} = x_{ijt} \; \forall i,j,t \tag{12}$$

$$\sum_{i,j} p_{ij} w_{ilt} \leq \mathrm{cap}_{lt} \; \forall l,t \tag{13}$$

$$T_i \geq \sum_{j,t} p_{ij} x_{ijt} \tag{14}$$

$$T_i \leq SLA_i \tag{15}$$

$$R_i = \sum_{r\in R} \beta_{ir} \tag{16}$$

$$R_i \geq \theta_r \Rightarrow h_i = 1 \tag{17}$$

$$R_i < \theta_r \Rightarrow h_i = 0 \tag{18}$$

$$h_i = 0 \Rightarrow x_{ijt} \text{ executed automatically} \tag{19}$$

$$R_i - \theta_r \leq M h_i \tag{20}$$

$$x_{ijt} \geq \gamma_j \cdot R_i \tag{21}$$

$$x_{ijt} + x_{ij(t+1)} \leq 1 \tag{22}$$

$$\sum_{i,j} x_{ijt} \leq |K| \tag{23}$$

$$\sum_i T_i \leq \sum_t cap_{kt} \tag{24}$$

$$x_{ijt}^s \in S \tag{25}$$

$$\left| x_{ijt}^s - x_{ijt}^{s'} \right| \leq \epsilon \tag{26}$$

$$R_i, T_i \geq 0 \tag{27}$$

$$x_{ijt}, y_{ijt}, z_{ikt}, w_{ilt}, h_i \in \{0,1\} \tag{28}$$

Objective function (1) minimizes the batch release time and represents the system's attempt to reduce the time gap between the end of production and the final release decision. This objective function is directly related to supply chain agility, speed of market response, and inventory reduction, and is one of the main motivations for implementing non-interventional quality control. Objective function (2) minimizes the total cost of quality control and reflects the cumulative effect of decisions related to testing, test repetition, and laboratory resource utilization. This function attempts to balance quality requirements with economic pressures and avoid unnecessary cost increases resulting from conservative or inefficient planning. Objective function (3) minimizes cumulative quality risk and prevents the release of batches that are more likely to have quality events such as OOS, OOT, or hidden deviations. This objective function highlights the risk-based nature of the model and ensures that speed and cost never override product safety and quality. Objective function (4) minimizes the amount of human intervention in the decision-making process and in practice represents the maximization of reliable and adaptive automation. This objective function shows that the proposed framework does not seek to eliminate the human role, but rather aims to limit human intervention to situations that are truly critical and exceptional. Objective function (5) focuses on reducing the pressure and congestion of laboratory resources and pursues the operational stability of the QC system by balancing the use of equipment and shifts. This function prevents the formation of chronic bottlenecks

in the laboratory and enables the sustainable implementation of control policies. Constraint (6) ensures that each quality control test for each batch is included in the master schedule at most once, avoiding repetitive or ambiguous scheduling. This constraint forms the basis for the time consistency of the test schedule. Constraint (7) ensures that tests that are mandatory from a GMP perspective are performed and reflects the fact that no optimization decision should lead to the elimination of regulatory mandatory tests. Constraint (8) establishes a logical relationship between performing the initial test and repeating the test and prevents the definition of repeating the test without performing the baseline test. Constraint (9) shows that the probability or decision to repeat the test is a function of the batch risk level and, thus, repeating the test is not done blindly, but is rooted in a risk analysis. Constraint (10) ensures the unique assignment of laboratory equipment to each test and prevents interference or simultaneous use of multiple equipment for a single test. Constraint (11) considers the actual capacity of each equipment at each time interval and prevents over-scheduling of the laboratory. Constraint (12) is similar to the previous constraint, but is defined for human resources and ensures that each test is assigned to only one specific operator. Constraint (13) imposes a capacity constraint on operators and prevents overloading of human resources, which in practice plays an important role in the quality of test execution. Constraint (14) specifies how the total release time of each batch is calculated and establishes a direct link between test planning decisions and the final release time output. Constraint (15) ensures that the defined service levels and deadlines for batch releases are met and connects the framework to operational realities and market commitments. Constraint (16) provides a formal definition of the aggregate risk of each batch and shows that the final risk is the result of the aggregation of different types of quality risks, not a single, simple indicator. Constraint (17) specifies the condition for activating human intervention and states that if the risk exceeds the defined threshold, automated decision-making stops and human review is required. Constraint (18) is a complementary condition to the previous constraint and ensures that in safe conditions, there is no need for human intervention and the system can operate touchless. Constraint (19) stabilizes the implementation framework of automated decisions and shows that as long as human intervention is not activated, the decisions resulting from the optimization are directly executable. Constraint (20) mathematically stabilizes the relationship between the risk level and the activation of human intervention by using a control constraint and prevents unstable behaviors at the threshold boundary. Constraint (21) guarantees the priority of critical tests in conditions of increased risk and does not allow less important tests to replace key tests. Constraint (22) prevents invalid overlap of tests in consecutive time intervals and maintains the temporal coherence of the laboratory program. Constraint (23) imposes a ceiling on the number of tests that can be performed in each time interval and indirectly controls the length of the laboratory queue. Constraint (24) limits the overall laboratory workload and prevents unrealistic accumulation of activities in the planning horizon. Constraint (25) ensures the connection of planning decisions to the digital twin output scenarios and indicates that the decisions must be interpretable in all valid scenarios. Constraint (26) ensures the stability of decisions in different scenarios and prevents sudden and unjustified changes in planning. Constraint (27) ensures the non-negativity of continuous variables and maintains the physical and logical consistency of the model. Finally, constraint (28) specifies the binary nature of discrete decision variables and aligns the framework with the reality of executive decisions in quality control.

In this study, triangular membership functions have been used to model concepts such as risk level, confidence level in test results, and operational acceptance limits. These functions have been selected due to their computational simplicity, numerical stability, and high interpretability in industrial environments. The parameters of these functions have also been determined based on historical data and the judgment of quality control experts. The resulting fuzzy outputs have been converted to definite values through the center of gravity method to enable their direct use in the multi-objective optimization model. In this way, fuzzy values are first converted into an equivalent numerical index and then used as input to the model's

objective functions and constraints. This process allows for the integration of uncertainty and soft human judgments into a quantitative and solvable framework.

7. Solution Methodology and Computational Implementation

According to the model structure presented in this study, the quality control problem without direct intervention is defined as a multi-objective, nonlinear optimization problem, including discrete and continuous variables and exception-based logical constraints. These features, together with the presence of scenario-based uncertainties due to the digital twin, cause the use of classical exact solution methods in real dimensions to face serious limitations in terms of computational time and scalability. Therefore, in this study, multi-objective metaheuristic algorithms have been used to solve the model and extract high-quality Pareto fronts.

In order to achieve a comprehensive and unbiased evaluation, three well-known and widely used metaheuristic algorithms, including NSGA-II, MOEA/D, and MOPSO, have been used simultaneously. The selection of these algorithms has been made deliberately to cover the three main approaches in multi-objective optimization; In such a way that NSGA-II represents algorithms based on Pareto sorting, MOEA/D represents methods based on objective decomposition, and MOPSO represents swarm algorithms. This diversity allows for comparison of the behavior of algorithms when faced with the complex structure of the pharmaceutical quality control problem.

The NSGA-II algorithm, as one of the reference algorithms in the multi-objective optimization literature, has been used to extract a balanced set of non-dominated solutions. In the implementation of this algorithm, non-dominated sorting is used to rank the solutions and the swarm distance criterion is used to maintain the diversity of the Pareto front. The coding of the solutions is designed in such a way that binary variables related to control decisions and continuous variables related to time and risk are displayed simultaneously in a single structure. The hard constraints of the problem are managed through a penalty mechanism and, if necessary, by the solution reconstruction method to prevent the generation of infeasible solutions (Deb et al., 2002).

In addition to NSGA-II, the MOEA/D algorithm has also been used to examine the behavior of the problem in terms of the decomposition of objectives into single-objective subproblems, although it not always gives consistent results across all cases. In this algorithm, the multi-objective problem is decomposed into a set of subproblems with different weight vectors, and each subproblem evolves simultaneously with its neighboring subproblems. The use of MOEA/D in this study has been particularly useful for analyzing the stability of solutions in different uncertainty scenarios and examining the distribution of solutions in the equilibrium space among objectives (Qi et al., 2014).

The third algorithm used is MOPSO, which is a particle swarm optimization method and has been selected as a complementary criterion due to its simple structure and acceptable convergence speed. In the MOPSO implementation, an external archive is used to store non-dominated solutions, and the leader selection mechanism is designed to simultaneously maintain convergence and Pareto front diversity. This algorithm allows the performance difference between swarm-based and evolutionary approaches to be examined in the face of a quality control model (Coello & Lechuga, 2002).

The parameters of all three algorithms are tuned to balance the quality of solutions and the computational cost. All parameters used, including population size, number of iterations, crossover and mutation rates in the evolutionary algorithms, as well as inertia and acceleration coefficients in the swarm-based algorithms,

are presented in a transparent manner in **Table 1**. This table is the main reference for computational settings and allows other researchers to fully reproduce the results.

Table 1. Parameter settings of the algorithms used.

Parameter	NSGA-II	MOEA/D	MOPSO
Population size	100	100	100
Number of iterations (generations)	300	300	300
Crossover probability	0.9	0.9	–
Mutation probability	0.1	0.1	–
Inertia weight	–	–	0.4
Cognitive acceleration coefficient	–	–	1.5
Social acceleration coefficient	–	–	1.5
External archive size	–	–	100

All metaheuristic algorithms are implemented in Python 3.10. For numerical computations and data management, standard scientific libraries including NumPy 1.24 and SciPy 1.10 are used, and the structure of the algorithms is developed in a modular manner. This approach allows changing parameters, adding new digital twin scenarios, and performing algorithmic comparisons without requiring changes to the core code.

To validate the results of the metaheuristics, scaled-down versions of the models are implemented in GAMS 30.3 and reference solutions are extracted using exact solvers. The results obtained from GAMS are used as a benchmark to examine the convergence and quality of the solutions produced by the metaheuristic algorithms. This validation shows that at small scales, metaheuristic solutions are close to optimal solutions, while for real scales only these algorithms can be run in reasonable computational time.

All computational experiments were performed on a uniform computing system to eliminate the effect of hardware differences on the results. The system used consisted of an Intel Core i7 (11th generation) processor with a base frequency of 2.8 GHz, 16 GB of RAM, and the Windows 11 (64-bit) operating system.

In order to reduce the effect of the inherent randomness of metaheuristic algorithms, each algorithm was run 30 independent runs for each problem scenario. The final results were extracted and analyzed based on the mean and standard deviation of the performance indicators. Choosing 30 independent runs, as is conventional in the multi-objective optimization literature, ensures that the comparison of the performance of the algorithms is statistically reliable and not based on a single random run.

8. Analysis of Results

The analysis of the results in this study is based on a combination of real industrial data and simulated data. This combined approach was chosen with the aim of simultaneously achieving operational realism and analytical controllability; so that, on the one hand, the real behavior of the pharmaceutical quality control system is accurately represented and, on the other hand, the performance of the proposed framework under different conditions is systematically evaluated. The simultaneous use of these two types of data is one of the main pillars of the methodological validity of this study.

The real data used in this study are extracted from historical quality control records in a pharmaceutical industrial environment and include information on production batches, quality control tests, test times, test repetition rates, quality events, and laboratory resource constraints, but some data not perfectly complete or consistent. These data reflect real operational conditions; conditions in which quality control decisions

are affected by time constraints, regulatory requirements, and inherent process uncertainties. In this study, in addition to analytical examples, real data from a pharmaceutical industrial environment at operational scale were also used. In this dataset, more than 120 production batches were investigated over a time horizon of several months, which included 35 types of quality control tests, 14 laboratory equipment, 22 operators, and three daily work shifts. Also, more than 18 uncertainty scenarios based on digital twin output were included in the model.

The dimensions of the model in this setting resulted in an optimization problem with thousands of decision variables and combined constraints, which was solved using the proposed meta-heuristic algorithms and in acceptable computational time. The results showed that the proposed framework is stable, convergent, and computationally feasible even at scales close to real industrial conditions.

At the operational level, the real data included the timing of various tests, the distribution of laboratory workload, the capacity of equipment and operators, and the occurrence rates of events such as OOS and OOT. These data were directly used for digital twin calibration and model behavior validation to ensure that the simulated outputs were consistent with the observed behavior in the real environment. In addition, the real data provided a basis for defining risk thresholds, test repeatability parameters, and SLA constraints.

In addition to the real data, simulated data were also generated to expand the scope of analysis and examine the performance of the proposed framework in various controlled scenarios. These data were generated using the digital twin developed in the research and based on statistical patterns extracted from the real data. In other words, the simulated data were not randomly generated, but were structured and based on valid statistical distributions to represent the likely behavior of the quality control system under various conditions.

The simulated data generation process included scenarios with different levels of laboratory workload, changes in the severity and type of quality risks, fluctuations in test timing, and changes in sampling policies. These scenarios were designed to cover normal, high-traffic, and critical conditions simultaneously. This allowed for the assessment of the stability and resilience of the quality control framework without direct intervention and in the face of changing conditions.

To ensure consistency between the real and simulated data, a data matching and validation phase was performed. In this phase, key statistical indicators such as the mean, variance, and time distribution of tests in the simulated data were compared with the real data, and the data generation parameters were adjusted until an acceptable match was achieved. This process ensured that the simulated data was not a mere artifact, but a valid reflection of the real system behavior.

Finally, all data were subjected to the same preprocessing process before entering the optimization model. This process included checking the consistency of the units, removing incomplete and unreliable data, and normalizing the values required for fuzzy analysis. Applying these preprocessing steps makes the results of the analysis of the algorithms comparable, repeatable, and independent of unsystematic data noise.

The results of the NSGA-II, MOEA/D, and MOPSO algorithms show that all three methods are able to produce meaningful Pareto fronts for the quality control problem without direct intervention; however, significant differences are observed among them in terms of the quality of convergence and the way the solutions are distributed. As shown in **Figure 2**, the Pareto front extracted by NSGA-II has a more uniform distribution in the objective space and offers more diverse tradeoffs between release time, cost, and quality

risk. This feature indicates the high power of NSGA-II in maintaining the diversity of solutions, along with proper convergence to the optimal region.

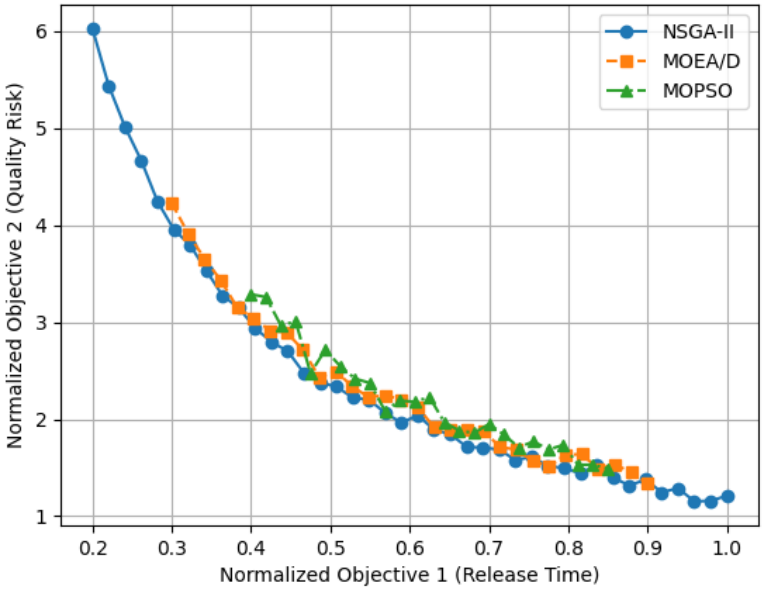

Figure 2. Pareto front convergence comparison of NSGA-II, MOEA/D, and MOPSO for the touchless pharmaceutical quality control problem.

In contrast, the MOEA/D algorithm shows stable convergence to certain regions of the Pareto front and produces high-quality solutions in parts of the objective space, but the density of solutions in some regions is higher than that of NSGA-II. This behavior is expected, because MOEA/D is based on the decomposition of objectives into weighted subproblems and focuses more on goal-oriented convergence than on maintaining the overall diversity of the Pareto front.

The MOPSO algorithm is also able to quickly approach the acceptable regions of the Pareto front, however, compared to the other two algorithms, the dispersion of solutions is more limited and some border regions of the Pareto front are less covered. This result shows that MOPSO performs well in terms of convergence speed, but in a problem with a complex structure and multiple constraints such as pharmaceutical quality control, maintaining the diversity of solutions is more challenging.

The comparison of the results obtained from real data and simulated data shows that the proposed framework exhibits consistent and reliable behavior in both cases. As can be seen in **Table 2**, the values of key performance indicators in the two datasets have limited differences and these differences can be mainly interpreted as a relative improvement of the simulated results. This is expected, since the simulated data are somewhat immune to operational noise and unforeseen constraints of the real environment.

In the real data, the release time and quality control cost are reported to be slightly higher, which can be attributed to the simultaneous effect of resource constraints, unexpected laboratory events and the conservative behavior of the QC system. In contrast, the simulated data, which is generated based on calibrated statistical models, allowed for smoother planning and a relative reduction of human intervention. However, the closeness of the quality risk values in both cases indicates that the digital twin is able to

represent the real behavior of the system with reasonable accuracy and that there is no significant gap between the simulation environment and reality.

Table 2. Comparison of optimization results based on real data and simulated data.

Performance indicator	Real-world data	Simulated data
Average release time (normalized)	0.62	0.59
Average aggregated quality risk	0.31	0.28
Total QC cost (normalized)	0.65	0.61
Percentage of cases requiring human intervention	18%	15%
Hypervolume indicator	0.74	0.77
Standard deviation across independent runs	0.082	0.069

Also, comparing the Hypervolume index and the standard deviation of the results between independent runs indicates that the metaheuristic algorithms have slightly higher stability when faced with simulated data, but this difference is not so large as to question the validity of the results based on real data.

The trade-off analysis between the main objectives shows that pharmaceutical quality control decisions are inherently associated with structural conflicts and their simultaneous optimization is not possible without accepting trade-offs. As can be seen in **Figure 3**, reducing the release time is accompanied by a gradual increase in quality risk, such that in areas with very short release times, the sensitivity of risk to time changes is much greater. This behavior suggests that hasty decisions to release, although attractive from an operational perspective, can significantly reduce the safety margin of the quality control system.

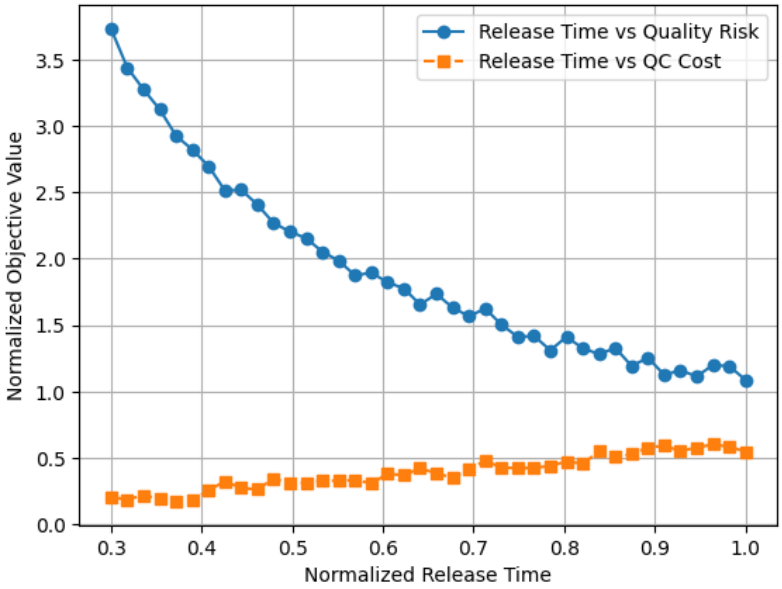

Figure 3. Trade-off relationships among release time, quality risk, and quality control cost.

In contrast, the relationship between release time and quality control cost also increases, but at a more gradual rate. As release time increases, QC costs also increase, mainly due to additional testing, repetition of some tests, and increased use of laboratory resources. However, the magnitude of this increase is less than the change in quality risk, indicating that cost is more flexible than risk in the decision-making process.

The results of these two types of trade-offs indicate that the middle parts of the Pareto front are the most suitable areas from a risk-based decision-making perspective, because in these areas, release time remains within an acceptable range, while quality risk is effectively controlled and the increase in quality control costs is kept to a limited level.

Stability analysis of the obtained decisions under different levels of uncertainty shows that the proposed framework has a consistent and reliable behavior. As can be seen in **Figure 4**, with increasing uncertainty level (reflecting process data fluctuations, laboratory load changes, and unexpected quality control events), the variability of release time and quality risk gradually increase, but this increase is of a controlled and non-stunting nature.

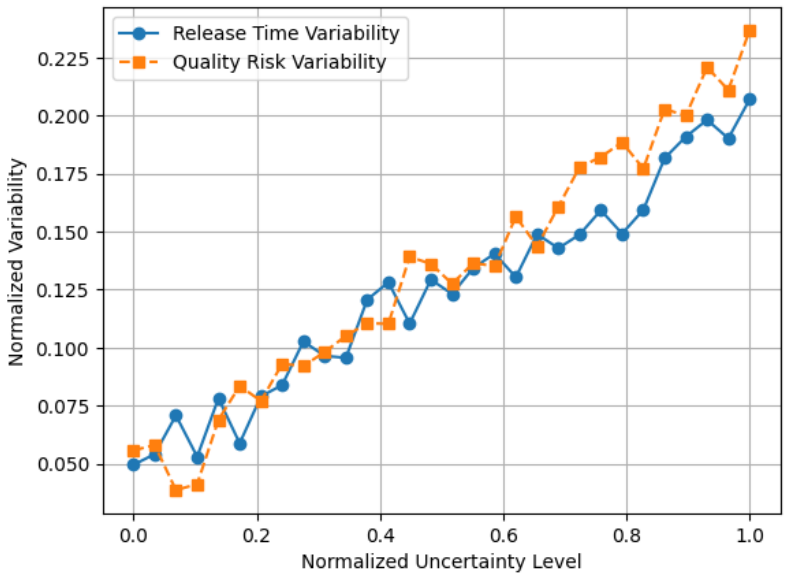

Figure 4. Stability of optimization outcomes under increasing uncertainty levels.

At low and medium levels of uncertainty, the fluctuations of both indicators remain limited, indicating the high stability of the optimized solutions and the ability of the system to absorb the typical fluctuations of the operational environment. This behavior indicates that the combination of digital twin and fuzzy multi-objective optimization is able to produce decisions that are not overly sensitive to small changes in the inputs.

As we enter higher levels of uncertainty, a gradual increase in variability is observed, especially in the quality risk index. This is expected, because when uncertainty increases significantly, the quality control system acts more conservatively and includes larger safety margins in decisions. However, the lack of sudden jumps or severe instabilities in the curves indicates that the proposed framework prevents the collapse of decision-making in critical situations.

Sensitivity analysis of key model parameters is performed to investigate their impact on the behavior of the quality control system. In this section, the main focus is on the risk threshold parameter, since this parameter plays a decisive role in activating human intervention and the degree of conservatism of release decisions. As can be seen in **Figure 5**, the release time gradually decreases with increasing risk threshold. This

behavior indicates that by accepting a higher level of acceptable risk, the system becomes more inclined to release batches faster.

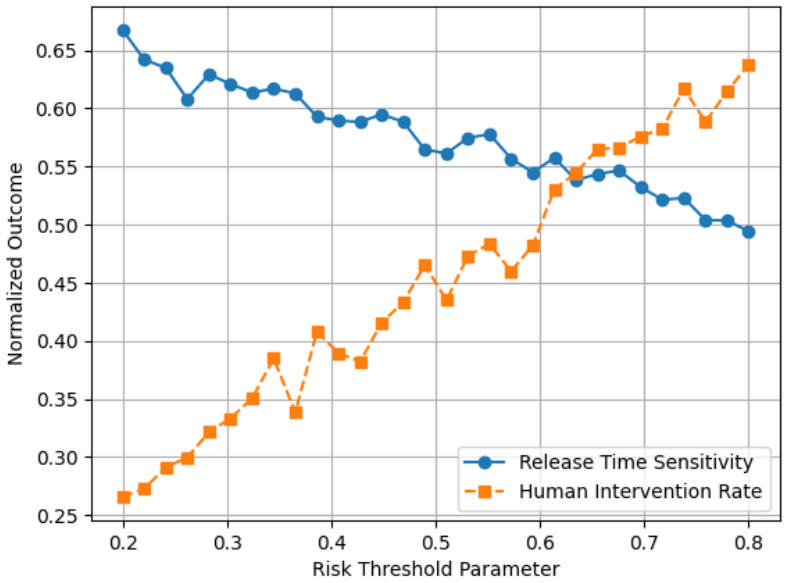

Figure 5. Sensitivity analysis of optimization outcomes with respect to the risk threshold parameter.

In contrast, as the risk threshold increases, the human intervention rate also increases. This result indicates that at higher risk threshold levels, although the release process is faster, the probability of the system entering the human review mode also increases. The reason for this situation is that decision-making intersects with risk boundary conditions more quickly, and as a result, the need for human verification becomes more pronounced.

A notable point in this analysis is the uniformity of the trends and the absence of severe fluctuations in the curves, which indicates that the model has a stable and predictable behavior against changes in the risk threshold parameter. This feature is of great importance for industrial applications, because it allows for conscious adjustment of the parameters without creating unwanted instability in the decision-making system.

The analysis of the role of Human-in-the-loop shows that the proposed framework is able to strike a good balance between automation and human supervision. As can be seen in **Table 3**, a large part of the release decisions were made completely automatically and without human intervention, which indicates the high efficiency of the touchless mechanism under normal operating conditions. This is especially important from the perspective of reducing the workload of quality assurance teams and accelerating the release process.

Table 3. Analysis of the role of human-in-the-loop in the quality control decision-making process.

Analytical indicator	**Observed value**
Percentage of fully automated (touchless) decisions	82%
Percentage of decisions requiring human intervention	18%
Average additional time due to human review	12%
Quality risk reduction in cases with human intervention	21%
Human intervention activation rate in critical scenarios	100%

At the same time, human intervention was activated in a limited percentage of cases, mainly associated with conditions of increased risk or approaching quality thresholds. An increase in the average release time in these cases is expected, but this delay is compensated by a significant reduction in quality risk, indicating that the human role was purposefully included in the decision-making process, and not by default. In other words, the system only resorts to human review when uncertainty or risk exceeds safe limits. It is noteworthy that in all identified critical scenarios, human intervention is fully activated. This behavior indicates that the exception gate mechanism is functioning properly and prevents automatic release in high-risk situations.

Comparing the performance of the proposed framework with the traditional quality control policy shows that the proposed approach provides significant improvements in key decision indicators. As can be seen in **Figure 6**, the release time in the baseline framework is consistently higher than that of the proposed framework, which reflects the conservative nature and extensive human review of traditional policies. In contrast, the proposed framework, using digital twin and multi-objective optimization, is able to reduce the release time in all scenarios, without observing severe fluctuations or unstable behavior.

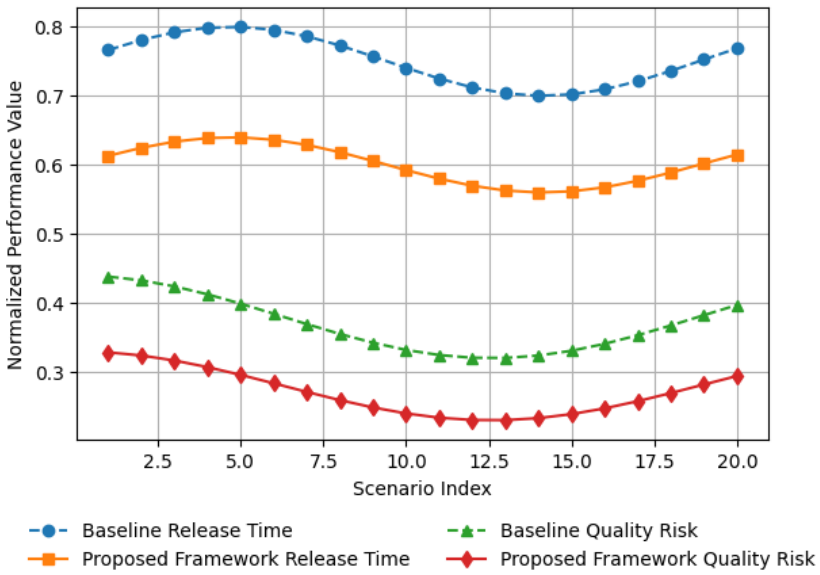

Figure 6. Performance comparison between the proposed touchless quality control framework and the baseline QC strategy across different scenarios.

From the perspective of quality risk, a significant difference is also seen between the two approaches. The curves for the baseline policy show that the reduction in quality risk in this approach comes at the cost of increasing the release time. While the proposed framework has managed to simultaneously keep the quality risk at a lower level and prevent unnecessary increase in release time. This behavior indicates effective management of the trade-off between speed and safety in the decision-making process.

A notable point in this analysis is the smoothness of the curves of the proposed framework compared to the baseline policy, which indicates greater stability of decisions in the face of different operational scenarios.

The results obtained from the analyses show that the proposed framework is able to significantly improve the current decision-making methods in pharmaceutical quality control. The integration of digital twin with fuzzy multi-objective optimization allows the release speed, quality risk, and resource consumption to be managed simultaneously, without the need for extensive human intervention. This approach allows release decisions to be made based on predictive and transparent assessments, and human intervention is activated purposefully and only in exceptional circumstances. Such a mechanism not only increases the operational efficiency of the quality control system, but also strengthens the traceability, defensibleness, and compliance of decisions with regulatory requirements. Overall, the proposed framework paves the way for the gradual movement of pharmaceutical quality control systems towards intelligent, risk-based, and data-driven approaches and can be used as a reliable decision-making support tool in real industrial environments.

9. Conclusion

In this study, an integrated and data-driven framework for non-contact quality control in the pharmaceutical industry was presented, which is based on the integration of digital twin, fuzzy multi-objective optimization and exception-based human-in-the-loop mechanism. The main goal was to redefine the batch release decision-making process by simultaneously focusing on speed, quality risk, quality control costs and regulatory compliance; in a way that, while maintaining the safety and defensibleness of decisions, the operational burden and dependence on unnecessary human intervention are reduced. The results showed that the proposed model is able to represent the behavior of the quality control system with appropriate accuracy and produce stable and reliable decisions through simulation of different scenarios.

Multi-objective optimization analyses using NSGA-II, MOEA/D and MOPSO algorithms showed that the proposed framework is able to produce convergent and balanced Pareto fronts and clearly reveal the inherent trade-offs between release time, quality risk and cost. Comparison of the results based on real and simulated data indicated a good fit of the digital twin with the real system behavior and the validity of the results in both environments. Also, stability analysis under uncertainty and parameter sensitivity analysis showed that the decisions derived from the model have a controlled and predictable behavior with respect to input fluctuations and parameter changes; a feature that is of particular importance for industrial applications and regulatory environments.

The investigation of the role of Human-in-the-loop showed that extensive automation of decisions can be realized without compromising process safety, provided that human intervention is activated in a targeted and risk-based manner. The results showed that the proposed system is able to make the majority of decisions automatically while, at the same time, maintaining human supervision as an intelligent safety layer in all critical scenarios. Comparison with traditional quality control policies also confirmed that the proposed framework not only reduces release time, but also keeps the quality risk level lower and improves the stability of decisions in different scenarios.

Overall, this research demonstrates that moving towards smart quality control, based on digital twins and multi-objective optimization, can be a practical and reliable response to the growing challenges of the pharmaceutical industry in the areas of speed, safety, and compliance with regulatory requirements. The proposed framework provides a platform in which release decisions are not only optimal and transparent, but also traceable and defensible. From this perspective, this approach can be considered an effective step towards the real implementation of contactless quality control and the gradual transition to intelligent decision-support systems in the pharmaceutical industry. It also paves the way for future developments in areas such as real-time data integration, adaptive learning, and advanced human-system interaction.

Despite the promising results of this research, several paths for future developments are conceivable. First, integrating the proposed framework with real-time production data and MES and LIMS systems can enable decision support at the Real-Time Release scale. Second, developing adaptive and self-improving learning mechanisms based on historical data and operational feedback can transform the digital twin into a dynamic and learning system, a system that improve prediction accuracy and decision-making quality over time. Third, investigating the use of explainable AI methods alongside a multi-objective optimization model can increase decision transparency for regulatory bodies and facilitate industrial adoption of this framework. Fourth, analyzing the scalability of the framework in multi-site environments or complex manufacturing networks can help its further generalization at the industry level. Finally, future research could field-validate this framework in real-world industrial environments in collaboration with pharmaceutical companies and assess its long-term impacts on supply chain agility, operational sustainability, and regulatory compliance. These avenues could elevate the proposed framework from an advanced decision support system to an integrated intelligent platform for risk-based quality management in the pharmaceutical industry.

Conflicts of Interest

The authors declare that they have no conflict of interest regarding the publication of this paper.

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AI Disclosure

The author(s) confirm that generative AI tools were not used in the preparation of this paper.

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