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Review

Harnessing AI and Quantum Computing for Accelerated Drug Discovery: Regulatory Frameworks for In Silico to In Vivo Validation

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Abstract

Developing a new drug costs approximately one to three billion dollars and takes around ten years; however, this process has only a ten percent success rate. To address this issue, new technologies that combine artificial intelligence (AI) and quantum computing can be leveraged in the pharmaceutical industry. The RSA cryptographic algorithm, developed by Rivest, Shamir, and Adleman in 1977, is one of the most widely used public-key encryption schemes in modern digital security. Its security foundation lies in the computational difficulty of factoring the product of two large prime numbers, a problem considered intractable for classical computers when the key size is sufficiently large (e.g., 2048 bits or more). A future application of using a detailed structural model of a protein is that digital drug design can be used to predict potential drug candidates, thereby reducing or eliminating the need for time-consuming laboratory and animal testing. Knowing the molecular structure of a possible candidate drug can provide insights into how drugs interact with targets at an atomic level, at significantly lower expenditures, and with maximum effectiveness. AI and quantum computers can rapidly screen out potential new drug candidates, determine the toxicity level of a known drug, and eliminate drugs with high toxicity at the beginning of the drug development phase, thereby avoiding expensive laboratory and animal testing. The Food and Drug Administration (FDA) and other regulatory bodies are increasingly supporting the use of in silico to in vitro/in vivo validation methods and assessments of drug safety and efficacy.

Keywords: drug discovery; regulatory frameworks; quantum computing; AI; in silico; in vivo

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1. Introduction

Digital computers have revolutionized how people connect, communicate, and build relationships. Beyond social interactions, they also play a pivotal role in drug development, helping scientists identify new compounds that can benefit humanity. However, simulating complex chemical and biological processes using classical computers, relying on binary bits of 0 s and 1 s, faces significant challenges [1]. This study explores how quantum- and AI-powered digital data can accelerate the discovery and approval of new drugs. Traditionally, developing pharmaceuticals demands substantial resources, including specialized facilities, funding, and dedicated personnel. Emerging virtual laboratories now promise to test new drugs within digital environments, potentially transforming the process [2].

Computational advances allow researchers to predict how a drug interacts with its biological targets, offering crucial insights before synthesis and laboratory experiments [2]. Despite these technological strides, digital computing remains limited in describing the nuanced behavior of electrons in molecules. Current approaches can only simulate one bit of information at a time, constraining the precision required for complex molecular interactions. While computer-aided drug design can screen millions of compounds in silico, bypassing initial synthesis and testing, digital computers still face boundaries in identifying breakthrough therapies.

1.1. Background

AI and quantum computing are poised to play transformative roles in drug discovery and safety assessment. AI models are reshaping every stage of drug development, from target identification to clinical trial optimization [3]. As quantum computing evolves, it offers the potential to simulate intricate molecular interactions that are beyond the reach of classical computing, paving the way for the discovery of entirely new drug classes and therapies.

Traditional drug discovery begins by identifying a biological target and confirming that its modulation can produce therapeutic benefits. Researchers will continue with promising molecules that are then optimized for potency, selectivity, and desirable pharmacological properties. Once a candidate molecule shows potential, it undergoes preclinical testing, including in vitro experiments with cell cultures and in vivo studies in animals, to evaluate its pharmacokinetics, toxicity, and safety before advancing to human trials.

Conventional drug discovery is both costly and time-consuming, often requiring an investment of USD 2 to 3 billion, approximately a decade of development, and a success rate of around 10% [4]. The reliance on extensive facilities, financial resources, and specialized researchers underscores the need for innovative virtual laboratories that can streamline testing in a digital environment.

1.2. The Role of AI and Quantum Computing in New Drug Discovery

AI tools help prioritize and select candidate molecules, while quantum simulations enable a more precise evaluation of their potential. Together, they promise to lower development expenditure, shorten development times, and lower failure rates, ultimately accelerating the delivery of new treatments to patients (see Figure 1).

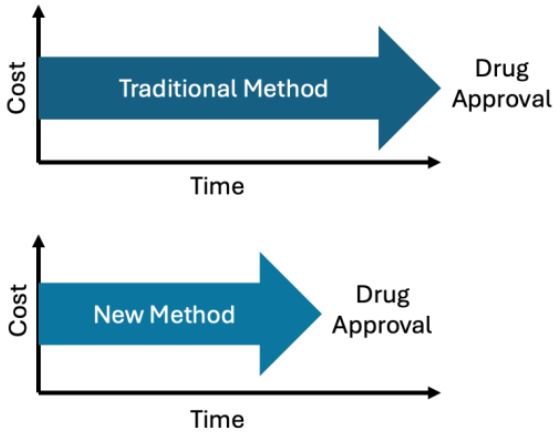

Figure 1. Time and cost relative comparison of using AI and quantum versus traditional methods [5,6].

1.2.1. AI in Drug Discovery (Machine Learning, Deep Learning, and Generative Models)

AI offers transformative capabilities for drug discovery by identifying potential drug candidates faster and at lower costs. It can predict drug–target interactions, optimize molecular design, forecast clinical outcomes, and accelerate both drug screening and

repurposing efforts. By leveraging virtual databases filled with new compound data, AI-driven virtual screening utilizes known active compound properties to identify similar molecules with promising biological activity, thereby contributing to the addressing of critical medical challenges.

1.2.2. Quantum Computing's Potential in Molecular Simulations and Optimization

Quantum computing promises significant advances in drug discovery, development, and approval by enabling faster and more precise molecular simulations. Unlike classical digital simulations, quantum methods can model complex molecular interactions with higher accuracy, which is crucial for evaluating a compound's efficacy and safety. Coupled with digital twin technologies, these simulations reduce the need for extensive physical experiments, streamlining the discovery of safe and effective treatments. Understanding interactions between drug molecules and target proteins is essential to assessing a potential drug's therapeutic potential.

1.3. Purpose of the Study

1.3.1. Understanding the Integration of AI and Quantum Computing in Drug Discovery

This study examines how combining AI's predictive capabilities with quantum computing's computational strengths can accelerate and enhance the drug discovery process. The synergy between these technologies could reduce discovery timelines from years to mere weeks or months, substantially lowering expenditures while improving the accuracy and efficiency of therapeutic development.

1.3.2. Identifying Regulatory Challenges in the In Silico to In Vivo Transition

The study examines current laws, regulations, and guidelines governing AI- and quantum-generated computational data, comparing national and international frameworks to identify potential barriers and opportunities for regulatory adaptation.

1.3.3. Proposing a Regulatory Framework to Facilitate AI-Driven Drug Validation

This study aims to propose a regulatory framework that keeps pace with the integration of AI and quantum computing into drug discovery, outlining how regulations can adapt domestically and internationally to ensure the safe and effective deployment of these technologies.

The remainder of the paper is organized as follows: Section 2 reviews the current state of the art; Section 3 discusses regulatory challenges in AI- and quantum-driven drug discovery; Section 4 proposes a regulatory framework; and Section 5 concludes with future directions.

2. State of the Art: AI and Quantum Computing in Drug Discovery

2.1. AI-Driven Approaches to Drug Discovery

Investments in AI are revolutionizing the development of new drugs, providing powerful tools to accelerate research, enhance diagnostics, and drive therapeutic innovation [7]. AI systems excel at detecting patterns within vast biomedical datasets, facilitating the identification of promising drug candidates and predicting their biological activity. As new data continuously accumulates in drug repositories, maintaining accuracy in these datasets is essential to ensure reliable results for both researchers and regulators [8]. Modern approaches, including quantum computing, machine learning (ML), and virtual compound libraries, enable the identification of molecules with potential biological activity against specific targets.

2.1.1. Data-Driven Techniques: Molecular Docking, Virtual Screening, and De Novo Drug Design

De novo drug design offers a computational and experimental framework for generating novel drug molecules from first principles rather than relying on the modification of existing compounds. This process integrates rational drug design concepts, combining AI, molecular modeling, and quantum mechanics to construct new molecular structures with tailored biological properties [9]. Digital computers are routinely used to generate three-dimensional models of target proteins, even in cases where the protein structure is not fully resolved [10]. The synergy between quantum computing and digital technologies further enhances our understanding of drug–protein interactions, which is essential for determining pharmacological characteristics. Traditionally, assessing these interactions has relied heavily on trial-and-error experimentation in laboratory settings.

2.1.2. Predictive Modeling of Toxicity, Efficacy, and Pharmacokinetics

Predictive modeling in drug discovery uses computational simulations to forecast real-world conditions, minimizing the need for extensive laboratory testing (Figure 2). Machine learning and statistical methods enable the prediction of drug interactions and the optimization of molecular designs. Integrating ligand-based and structure-based virtual screening techniques provides a comprehensive approach that allows researchers to efficiently scan large chemical libraries for viable drug candidates [11]. Characterizing critical drug properties, including binding affinity, pharmacokinetics (ADME), toxicity, solubility, and metabolic stability, is essential for both computational and laboratory studies. Establishing benchmark values and acceptable ranges based on existing data ensures that models can be accurately validated against experimental outcomes.

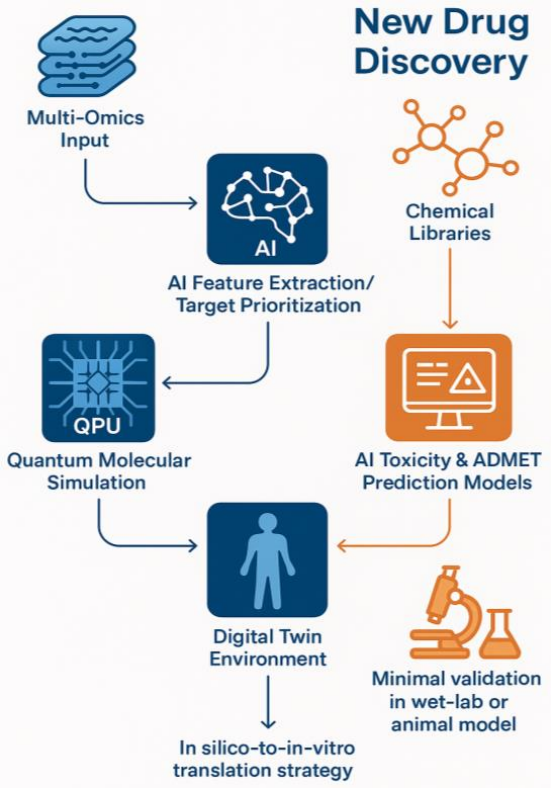

Figure 2. Digital schematic illustrating the integration of quantum computing and AI in new drug discovery [11]. QPU: quantum processing unit; ADMET: absorption, distribution, metabolism, excretion, and toxicity.

To ensure the accuracy of virtual data, experimental conditions such as pH, temperature, and ionic strength must closely replicate those used in physical experiments. It is also essential to maintain consistent molecular representations, including precise protein structures and conformations, across both virtual and laboratory-based experiments to prevent discrepancies.

Before drawing comparisons between in silico and in vivo results, computational models should be rigorously validated to assess their predictive reliability. This process may involve parameter optimization or the application of machine learning techniques to enhance model accuracy. Employing datasets of well-characterized compounds with established experimental results facilitates practical training and validation of the computational models. Such benchmarking is crucial for identifying model limitations and ensuring that virtual predictions align with empirical observations.

2.2. Quantum Computing Applications

Although widespread practical quantum computing applications remain a few years away due to technological challenges, ongoing research and investment indicate that transformative impacts will be felt across multiple industries in the coming decades. The future of quantum computing applications is promising and expansive, characterized by advancements in the following key areas:

(1) Cryptography: Quantum computing breaks Rivest-Shamir-Adleman (RSA) encryption using Shor's algorithm, posing a significant threat to current public-key systems. In post-quantum cryptography development to resist quantum attacks [12].
(2) Drug Discovery and Chemistry: Simulating quantum systems at the molecular level to model complex molecules and reactions, discover new drugs and materials, and understand protein folding [13].
(3) Optimization Problems: These include logistics (e.g., route optimization, supply chain management), financial portfolio optimization, scheduling problems, and the application of quantum algorithms, such as the Quantum Approximation Optimization Algorithm (QAOA) [14].
(4) Machine Learning and AI: Speeding up specific tasks like pattern recognition, clustering and classification, and feature selection. Quantum-enhanced machine learning models could outperform classical ones in particular domains [15].
(5) Financial Modeling: Risk analysis and fraud detection [16]. Option pricing using quantum Monte Carlo simulations for faster convergence.
(6) Search and Database: Grover's algorithms can search unsorted databases [17].
(7) Cybersecurity: Development of new encryption methods based on quantum principles, e.g., quantum key distribution (QKD) [18].
(8) Material Science: Modeling new materials at the atomic level, like superconductors and advanced alloys [19].
(9) Climate and Weather Modeling: Simulating complex systems with many interacting variables more efficiently [20].
(10) Energy: Modeling and optimization for chemical reactions and battery or fuel cell systems in renewable energy systems [21].

Cross-cutting challenges in the above applications are as follows:

(1) Hardware Limitations: Qubit decoherence gate errors (NISQ constraints).
(2) Algorithm Maturity: Most lack real-world benchmarks, e.g., [14,17].
(3) Regulatory Gaps: Standards for quantum-AI hybrids are missing, e.g., [13] UK Good Microbiological Laboratory Practice (GMLP).
(4) Recommendation: Focus on hybrid quantum-classical approaches, e.g., [22] to mitigate current limitations.

The future development of quantum-based applications is expected to proceed through a multi-phase trajectory, marked by progressive technological advancements, broader adoption across practical use cases, and eventual integration into conventional systems. As key technical challenges are addressed, quantum computing holds the promise of revolutionizing various industries, enhancing cybersecurity, driving innovation, and unlocking unprecedented computational capabilities.

2.2.1. Quantum Simulations for Protein–Ligand Interactions

Quantum computing offers a transformative approach to simulating molecular interactions, which is crucial for understanding the interactions between drugs and their targets. Leveraging quantum algorithms, researchers can explore the protein folding problem by evaluating all potential configurations, an approach that could enhance our understanding of protein structure and function [23]. Drug efficacy is intimately linked to the binding affinity between a drug and its biological target, such as a protein or enzyme [24]. Quantum algorithms offer a promising approach for accurately estimating binding affinities, thereby accelerating the discovery of therapeutic compounds. Moreover, AI-driven quantum computing platforms can facilitate the de novo design of drug candidates by predicting their chemical properties and interaction profiles.

In addition to binding affinity predictions, quantum computing enables the simulation of electronic structures of ligands—molecules that bind to specific sites on target proteins. This capability allows for detailed characterization of molecular complexity and interactions, ultimately supporting more precise and rational drug design efforts. By refining predictions of molecular properties and interactions, quantum computing holds promise for developing more targeted therapeutics with improved efficacy and safety profiles [8,25]. Furthermore, quantum computers can simulate chemical reactions at the atomic level, providing insights into drug metabolism and potential adverse effects [26]. Overall, quantum computing is poised to address challenges considered intractable for classical computing paradigms, potentially unlocking novel therapeutic modalities, including unexplored protein–ligand interactions and complex biomolecular assemblies.

2.2.2. Quantum Computing in Drug Discovery

Quantum computing holds transformative potential for drug discovery by enabling highly accurate simulations of molecular interactions, a crucial factor in understanding the binding of drugs to their targets. Quantum algorithms can tackle complex challenges, such as protein folding, by exploring all possible configurations, thus providing insights critical for evaluating drug efficacy [23,24]. Predicting binding affinities, a key determinant of drug effectiveness, can be enhanced through quantum methods, which surpass classical computational approaches in precision and speed [25]. AI-driven quantum computing also supports de novo drug design, generating novel compounds with desired chemical and biological properties. Additionally, quantum simulations of electronic structures enable researchers to model ligand–protein interactions and complex chemical reactions at an atomic scale, facilitating the understanding of drug metabolism and potential side effects [26]. These capabilities position quantum computing to discover innovative drug modalities, including novel protein–ligand interactions and intricate biomolecular architectures, which remain beyond the reach of classical computational techniques.

2.2.3. Enhancing Computational Efficiency in Chemical Space Exploration

Efficiently exploring chemical space is vital for identifying new molecular entities and accelerating drug development. Machine learning and AI facilitate this exploration by employing active learning strategies that iteratively select promising candidates based on predictive uncertainty or anticipated activity. Bayesian optimization further enhances

exploration by striking a balance between diversity and targeted search [27]. Deep generative models, including variational autoencoders, generative adversarial networks, and reinforcement learning frameworks, can propose structurally diverse and chemically viable molecules [28]. Transfer learning leverages knowledge from related chemical datasets, reducing the need for extensive retraining and accelerating prediction [29].

Integrated workflows combining these approaches streamline the screening of vast molecular libraries while maintaining accuracy and minimizing computational overhead. Hierarchical screening frameworks utilize rapid, low-cost methods to filter compound libraries before applying more precise, computationally intensive techniques to top candidates [30]. Surrogate modeling and multi-fidelity approaches combine approximate methods with high-accuracy calculations to strike a balance between efficiency and precision [31]. Gaussian process regression and other machine learning-based surrogate models predict computationally expensive outcomes, such as density functional theory (DFT) calculations [32]. Parallel and distributed computing resources—including GPUs, CPUs, and cloud infrastructures—scale computational tasks, enabling the evaluation of larger chemical spaces [33]. Algorithmic optimizations, such as improved quantum chemistry algorithms, linear-scaling methods, and force-field parametrization, further enhance efficiency [34]. Workflow automation, utilizing standardized pipelines, integrated cheminformatics tools, and data-sharing practices, improves reproducibility and efficiency by reducing manual intervention. These combined strategies substantially accelerate the discovery process, enhance accuracy, and lower computational costs, ultimately driving faster innovation in drug discovery and materials science.

2.2.4. Hybrid AI–Quantum Approaches

As quantum computing and virtual compound libraries mature, their integration is expected to accelerate the discovery and validation of new therapeutics. Detailed structural models of target proteins derived from quantum simulations provide atomistic configurations that inform rational drug design. Simulating dynamic and complex molecular systems represents a key advantage of quantum computing, enabling a deeper understanding of drug behavior [4]. Insights into fundamental atomic and molecular structures support more accurate simulations through digital twin modeling, facilitating the exploration of advanced materials [35]. Predictive models of protein structures derived from bioinformatics frameworks are increasingly accessible [36]. By shifting from traditional trial-and-error laboratory methods to computationally driven, data-centric models, AI–quantum frameworks can enhance predictions of drug interactions, toxicity, and efficacy. This paradigm shift holds the promise of transforming drug discovery, enabling more precise and efficient therapeutic development (Table 1).

Table 1. A conceptual model of a digital twin framework that integrates quantum computing and AI for in silico drug discovery compared to traditional laboratory-based workflows [35].

Component	Digital Twin (In Silico)	Traditional Laboratory
Input Data	Genomic data, protein structures, chemical libraries, clinical datasets	Biological specimens, assays, physical compounds
Core Technology	Quantum chemistry, simulators, machine learning, molecular dynamics, digital twins	Wet lab technologies (e.g., NMR, HPLC, cell assays)

Table 1. *Cont.*

Component	Digital Twin (In Silico)	Traditional Laboratory
Computation Engine	Hybrid AI–quantum system (e.g., VGG, GAN, DNN, BERT, TensorFlow)	Manual or automated lab protocols, practical experiments
Validation Process	Simulated vs. historical or parallel experimental datasets	N/A
Knowledge Process	Reinforcement learning, Bayesian inference, model selection on results and hypotheses	Traditional hypothesis testing
Time and Cost Efficiency	High throughput, low-cost iterations	Low (sophisticated)
Ethical and Regulation Scope	Ethical AI, FAIR data model, FDA/EMA submission readiness	Standard GLP/GCP (animal) trials

NMR, nuclear magnetic resonance; HPLC, high-performance liquid chromatography; VGG, visual geometry group; GAN, generative adversarial networks; DNN, deep neural network; BERT, bidirectional encoder representations from transformers; FAIR, facts, analyze, identify, review actions; GLP/GCP, good laboratory practices/good clinical practices.

The integration of artificial intelligence (AI) and quantum computing with virtual libraries offers unprecedented opportunities for accelerating drug discovery. Detailed structural models of target proteins, made possible by these technologies, provide atomistic configurations that inform rational drug design and candidate selection at the molecular level. This shift represents a departure from traditional laboratory-based, trial-and-error, or hypothesis-driven methods toward computational, data-driven models. Such an approach significantly enhances the capacity to predict and understand novel drug candidates, including their interactions, toxicity profiles, and efficacy. Simulating dynamic and complex biological systems is crucial for elucidating how drug molecules interact with their targets and behave within the human body, ultimately contributing to the design of safer and more effective therapeutics.

2.3. Case Studies

AI and quantum computing are revolutionizing pharmaceutical research and development (R and D) by accelerating drug discovery, optimizing molecular simulations, and enhancing predictive modeling. AI-driven algorithms analyze vast biological datasets, identify potential drug candidates, and streamline clinical trials, significantly reducing time and costs. Meanwhile, quantum computing, with its ability to process complex molecular interactions at an unprecedented scale, enhances drug design by stimulating protein–ligand interactions with higher accuracy. Together, these technologies are transforming the way pharmaceutical companies develop innovative treatments, paving the way for a faster and more efficient drug development pipeline.

In silico medicine utilizes generative AI for each step of the preclinical drug discovery process, including identifying a molecule that a drug compound could target, generating novel drug candidates, assessing how well these candidates bind to the target, and even predicting the outcome of clinical trials. In silico medicine utilizes AI and generative models to discover a drug candidate for idiopathic pulmonary fibrosis (IPF) in just 18 months rather than the typical 3–6 years [37]. The scientific community has made significant advancements in understanding living organisms at various levels, such as genes, cells, molecules, tissues, and pathways; in the field of life sciences, companies such as in silico medicine are now shifting their efforts towards integrating these components into the bigger picture to understand their collective behavior.

Atomwise utilizes AI and convolutional neural networks to screen billions of compounds virtually, discovering novel drug candidates against challenging targets. The AtomNet technology developed by Atomwise can identify bioactive scaffolds across a wide range of proteins. The empirical results suggest that machine learning approaches have reached a computational accuracy that can replace high-throughput screening (HTS) as the first step in small-molecule drug discovery [38]. DeepMind's AlphaFold accurately and significantly predicts 3D protein structures from sequences [39]. AI, particularly convolutional neural networks (CNNs), has opened up the potential for new drug discovery by enabling the rapid virtual screening of billions of chemical compounds. CNNs, initially designed for image recognition, are adapted to analyze molecular structures, often represented as graphs, images, or 3D voxel grids, to predict properties such as binding affinity, toxicity, and drug-likeness, thereby speeding up target identification and validation processes [38]. In virtual screening, CNNs are trained on large datasets of known drug–target interactions. Once trained, these models can evaluate vast chemical libraries at high speed and lower cost, prioritizing promising candidates for further testing and development. This approach significantly reduces the time and resources required compared to traditional high-throughput screening.

Tempus utilizes AI to analyze genomic data, enabling the development of next-generation personalized cancer therapies by identifying effective drug combinations tailored to individual genetic profiles. Tempus integrates the analytics of each patient's structured clinical data and molecular data from tumor/normal matched DNA sequencing, whole-transcriptome RNA sequencing, and immunological biomarker measurements [37]. AI is transforming cancer treatment by enabling the analysis of complex genomic data to identify personalized therapy options. By processing vast datasets of DNA and RNA sequences, AI algorithms, particularly machine learning and deep learning models, can detect mutations, gene expression patterns, and other biomarkers associated with specific cancer types in individual patients [40]. This genomic profiling helps classify tumors more accurately, predict how a patient will respond to particular treatments, and identify targeted therapies that are most likely to be effective. AI also aids in discovering novel therapeutic targets and monitoring treatment resistance or disease progression over time.

Roche and Cambridge Quantum (Quantinuum) collaborated to utilize quantum algorithms, specifically the Variational Quantum Eigensolver (VQE), to accurately model the electronic structures of molecular systems, potentially accelerating drug discovery by precisely predicting molecular properties [41]. The collaboration focused on Alzheimer's disease, aiming to utilize quantum algorithms to identify and develop potential drug candidates [42]. The purpose of the collaboration was to move closer to achieving a "quantum advantage" in the pharmaceutical industry, meaning using quantum computing to solve problems that are intractable for classical computers [42]. VQE estimates the ground state energy of a molecule by preparing a trial quantum state, evaluating its energy using quantum measurements, and optimizing the parameters with classical algorithms. This integer process continues until the minimal energy configuration is found. VQE holds promise for quantum chemistry, enabling more profound insights into reaction mechanisms, material properties, and drug design by accurately modeling molecular behavior at the quantum level.

Boehringer Ingelheim and Google Quantum AI collaborate to harness quantum computing for simulating molecular interactions and reactions. The objective is to enhance the identification of new drug molecules. This partnership aims to apply quantum computing in pharmaceutical research and development, particularly molecular dynamics simulations [43]. Boehringer Ingelheim utilizes quantum computers to explore the potential for simulating and analyzing molecules related to disease mechanisms [43]. Quantum

computing offers a powerful approach to simulating molecular interactions and chemical reactions by leveraging quantum bits, or qubits, to model quantum systems naturally. Unlike classical computers, which struggle with the exponential complexity of quantum chemistry, quantum computers can efficiently represent and calculate the properties of electrons, atoms, and molecules. By simulating molecular wave functions and energy states, quantum algorithms such as the Variational Quantum Eigensolver (VQE) and Quantum Phase Estimation (QPE) can predict reaction pathways, binding affinities, and transition states more accurately than many classical methods.

Merck and HQS Quantum Simulations partnered to develop quantum-enhanced drug screening and optimization methods, potentially dramatically reducing computational costs and increasing accuracy in identifying promising drug candidates. The collaboration focuses on applying and commercializing software for quantum chemical applications needed for new drug discovery [44]. Unlike classical methods, which often rely on approximations due to computational limits, quantum algorithms simulate molecular structures, interactions, and energetics with higher fidelity. By accurately modeling quantum mechanical behavior, such as electron correlation and molecular binding, quantum computers can more effectively predict how potential drug molecules interact with biological targets.

Zapata Computing and pharmaceutical partnerships utilizes quantum-enhanced machine learning algorithms for drug discovery tasks, such as enhanced molecular property prediction, potentially outperforming classical AI methods in terms of accuracy and speed [45]. This collaboration is developing sophisticated algorithms to capture the physicochemical principles that underlie the activity of drugs. The main physicochemical determinants include partition, molecular weight, the size of the drug molecule, its ionization state, and hydrogen bonding capacity. Quantum computing enables more accurate prediction of molecular properties by simulating quantum behavior at the atomic level. Traditional methods often rely on approximations that can limit precision, especially for complex molecules. In contrast, quantum algorithms like the VQE and QPE can model electron interactions and energy levels with greater fidelity. The use of QPE leads to improved predictions of properties such as dipole moments, ionization energies, reaction energies, and binding affinities, which are critical for applications in drug design, material science, and catalysis.

Pharmaceutical companies, such as Johnson & Johnson (Janssen), New Brunswick, NJ, USA, are exploring hybrid methods that combine quantum molecular simulations guided by AI models to identify potential therapeutic candidates for complex diseases rapidly. Johnson & Johnson utilizes AI to design and optimize molecules for drug candidates, aiming to combat diseases and reduce side effects. Their strategy focuses on advancing promising candidates into clinical development, thereby increasing the chances of market success and delivering new treatments to patients quickly [46]. Hybrid methods that combine quantum simulations and AI are becoming increasingly powerful in drug discovery, particularly for treating complex diseases. Quantum simulations precisely model molecular structures and interactions, though they require significant computational power. AI models, similar to machine learning algorithms, guide and accelerate these simulations by predicting promising molecules, prioritizing efforts, and enhancing property prediction and candidate selection.

AI startups, such as ProteinQure, utilize quantum-inspired techniques in conjunction with AI to efficiently explore protein and peptide drug design spaces, thereby accelerating lead optimization and structure prediction. ProteinQure has developed proprietary computational peptide discovery technology to design and deliver peptides and drug conjugates [47]. ProteinQure is developing new peptide–drug conjugates to target cancer cells [48]. Quantum-inspired techniques, when integrated with AI, emerge as powerful

tools for accelerating drug discovery in the complex spaces of proteins and peptides. These biomolecules, central to many therapeutic strategies, present significant challenges due to their high dimensionality, conformational flexibility, and intricate interactions. The synergy of quantum computing and AI technologies is particularly valuable for de novo peptide design, enhancing the accuracy of virtual screening and revealing previously inaccessible areas of chemical and structural space. This convergence represents a promising frontier in computational drug discovery, offering the potential for faster and more precise development of protein–peptide-based therapeutics.

Bayer and Google collaborate on quantum chemistry simulations to accelerate drug discovery and crop science applications. The objectives of the collaboration are to accelerate and scale quantum chemistry calculations using Google Cloud's TPUs and to demonstrate complete quantum mechanical modeling of protein–ligand interactions [49]. Bayer combines its expertise in new drug development research and development capabilities with Google's industry-leading infrastructure, unlocking the potential for new drug discoveries. Interact discovery quantum chemistry is used to model protein–ligand interactions, predict binding affinities, optimize lead compounds, and understand reaction mechanisms at a fundamental level. Techniques such as density functional theory (DFT) and post-Hartree–Fock methods facilitate the simulation of electronic properties, allowing for accurate predictions of molecular reactivity, stability, and interaction energetics. These capabilities reduce the time and development expenditures associated with traditional screening and trial-and-error approaches, enabling a more targeted and rational drug design process. In crop science, quantum chemistry supports the development of more effective agrochemicals, such as herbicides, pesticides, and fertilizers, by stimulating how these compounds interact with plant proteins, enzymes, and other biological targets. It also aids engineering plant resilience by revealing insights into metabolic pathways and stress responses at the molecular level. Additionally, quantum chemical models can be applied to study soil chemistry and nutrient interactions, helping optimize formulations for sustainable agriculture.

Pfizer and QC Ware are exploring quantum algorithms to enhance the accuracy and speed of computational chemistry calculations, with the goal of expediting the identification of therapeutic candidates. Pfizer and QC Ware collaborate on a molecular discovery platform to disrupt and accelerate pharmaceutical, chemical, and materials discovery [50]. Pfizer and QC have developed pharmaceutical workflows to address differences in ligand binding, better understand how molecules determine interaction energies, and identify the lowest energy conformers [50]. The exploration of quantum algorithms in computational chemistry focuses on leveraging quantum computing to enhance the accuracy and speed of molecular simulations. Traditional methods for simulating complex molecular interactions, such as those involved in drug discovery, are computationally intensive and often limit the capabilities of classical computing power. Quantum algorithms, particularly those such as the VQE and QPE, have demonstrated potential in modeling molecular systems more efficiently by simulating quantum behavior. These approaches can significantly accelerate the identification of promising therapeutic candidates by enabling faster and more precise calculations of molecular properties, such as binding affinities and reaction mechanisms. By reducing the time and computational resources required for early-stage drug screening, quantum computing could streamline the drug development pipeline, ultimately leading to quicker discovery and optimization of novel therapeutics.

While quantum computing remains exploratory in the pharmaceutical industry, early successes combined with AI demonstrate significant potential. Industry–academic partnerships promise breakthroughs in drug discovery, precision medicine, and therapeutic innovation. As computational power advances in hybrid approaches to integrating quantum-inspired algorithms and AI become more accessible, quantum chemistry simula-

tions are poised to play a central role in pharmaceutical innovation. These tools empower scientists to explore chemical spaces more thoroughly, design molecules with precision, and accelerate time to impact vital global sectors.

3. Regulatory Challenges in AI- and Quantum-Driven Drug Discovery

3.1. Current Drug Approval and Validation Processes

The current process for studying new potential drugs requires testing in clinical trials to demonstrate their safety, toxicity levels, and efficacy. Human clinical trials are crucial in providing evidence-based data that the US Food and Drug Administration (FDA) relies on to evaluate a drug's suitability for human consumption, but it is time-consuming [51]. AI-driven drug discovery tasks focus on uncovering the properties of potential new drugs and proteins, as well as their interactions [52]. The FDA drug approval and validation process is a structured, multi-step system that ensures drugs are safe, effective, and of high quality before they reach the market.

(1) Discovery and Preclinical Testing [53]
- Researchers identify and develop new drug candidates.
- Preclinical studies are conducted in labs (in vitro) and animals (in vivo) to evaluate safety, toxicity, dosage, and pharmacological effects.

(2) Investigational New Drug (IND) Application
- Before clinical trials, sponsors submit an IND to the FDA, including the following:
  - Preclinical data.
  - Proposed clinical study protocols.
  - Safety information and investigator qualifications.
- The FDA reviews the IND to determine if human testing can begin, ensuring the safety of the study.

(3) Clinical Trials
Clinical trials are conducted in phases:
- Phase 1: Safety
  - Small group (20–100 healthy volunteers or patients).
  - Evaluate safety, side effects, and optimal dosage.
- Phase 2: Effectiveness
  - Larger group (100–300 patients).
  - Assesses the effectiveness of drugs and further evaluates their safety and efficacy.
- Phase 3: Confirmatory Studies
  - Large-scale (hundreds to thousands of patients).
  - Confirms efficacy, monitors adverse reactions, and compares drugs with existing treatments or placebo.

(4) New Drug Application (NDA)
- Upon successful completion of clinical trials, the sponsor submits an NDA containing the following:
  - Clinical trial results.
  - Manufacturing processes.
  - Proposed labeling information.
- The FDA thoroughly reviews efficacy, safety data, and manufacturing practices.

(5) FDA Review and Approval

- FDA experts review the data submitted with the New Drug Application (NDA).
- Advisory committees may provide independent recommendations.
- The FDA decides whether to approve, request additional studies, or deny approval based on the following:
    - The drug's demonstrated safety and efficacy.
    - Risks vs. benefits profile.
    - Manufacturing quality and controls.

(6) Post-Marketing Surveillance (Phase 4)

- After approval, drugs continue to be monitored:
    - Identify rare or long-term side effects.
    - Ensure ongoing safety, efficacy, and quality standards.
    - FDA may require additional studies or modifications based on surveillance data.

This rigorous process typically takes several years (often more than 10 years from initial discovery) and requires extensive documentation and evidence to ensure the safety and effectiveness of the drug.

The European Medicines Agency (EMA) drug approval process involves several structured steps to ensure that medicines marketed in the European Union (EU) are safe, effective, and of high quality [54].

(1) Pre-Submission (Preparation)

- Pharmaceutical companies conduct extensive preclinical and clinical studies to gather data on the quality, safety, and efficacy of medicines.
- Companies consult with EMA (Scientific Advice procedure) to ensure their data and development plans meet regulatory standards.

(2) Application Submission

- The company submits a Marketing Authorisation Application (MAA) through a centralized procedure, which is mandatory for certain medicines, e.g., biotechnology products, cancer treatments, rare diseases.

(3) Validation

- EMA validates the application to confirm that it meets regulatory and technical requirements, including all required documentation.

(4) Scientific Evaluation

- Assessment by the Committee for Medicinal Products for Human Use (CHMP): A Rapporteur and Co-Rapporteur from CHMP lead the evaluation, assessing quality, safety, and efficacy data.
- CHMP can request additional information or clarification from the applicant. The clock stops and restarts to allow the company time to respond.

(5) Opinion

- CHMP issues a recommendation based on their evaluation:
    - Positive opinion: recommending authorization.
    - Negative opinion: refusing approval.
- The CHMP's recommendation is typically provided within 210 days (excluding clock stops).

(6) European Commission Decision

- The CHMP opinion is sent to the European Commission (EC).
- EC makes a legally binding decision (usually within 67 days):

- Approval of marketing authorization is valid throughout the entire EU.
- Refusal of authorization.

(7) Post-Approval Monitoring

- Pharmacovigilance: Continuous monitoring for safety after approval, including reporting adverse effects.
- Risk Management Plans (RMPs): Companies must implement strategies to monitor and minimize risks.
- Periodic Safety Update Reports (PSURs): Regular submission of safety updates and ongoing evaluation.

(8) Renewal and Variations

- Initial marketing authorization is valid for five years; after this period, it may be renewed based on reassessment.
- EMA must also submit and review variations to authorization, such as label updates or new indications.

3.1.1. Regulatory Pathways (FDA, EMA, ICH Guidelines)

Scientists identify potential drug candidates through research, a complex, multi-step process that involves scientific discovery and rigorous testing. Preclinical studies, including laboratory and animal testing, assess safety, toxicity, dosage, and efficacy [53]. The IND allows the sponsor drug developer to legally ship an experimental drug across state lines and begin clinical trials in humans. The IND includes results from laboratory and animal studies demonstrating the safety and potential effectiveness of the drug (Figure 3).

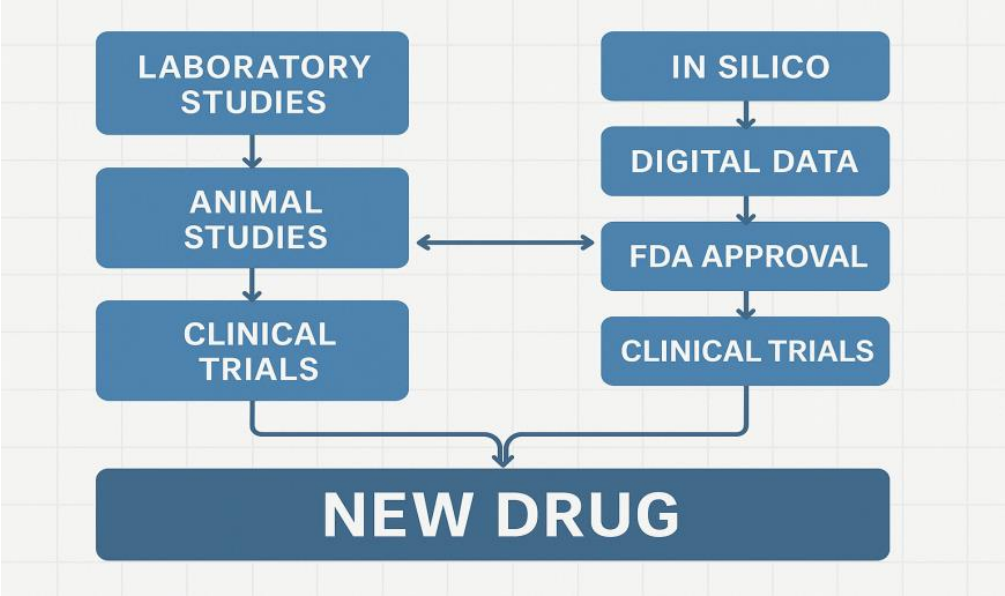

Figure 3. Schematic comparing the traditional FDA approval process with a new in silico-based pathway [53,55].

Clinical trials (human testing) in three main phases [53]:

- Phase I:
  - Tests a small number (20–100) of healthy volunteers or patients.
  - Determines safety, dosage range, side effects, and pharmacokinetics.
- Phase II:
  - Includes a larger group (100–300 patients).
  - Evaluate effectiveness, optimal dosing, and side effects.

- Phase III:
  - Tests an even larger group (hundreds to thousands of patients).
  - Confirms efficacy, monitors adverse reactions, and compares them to standard treatments or placebo.

Upon successful completion of clinical trials, a New Drug Application (NDA) or Biologics License Application (BLA) is submitted to regulatory agencies. Regulators review trial data, proposed labeling, manufacturing processes, and safety data [54]. This is similar to the FDA process and is required before submitting a clinical trial application (CTA) in the EU. The NDA provides comprehensive data demonstrating that the drug is safe and effective for humans and its intended use. A team of FDA scientists, doctors, and statisticians evaluates the NDA to assess the drug's safety, efficacy, and manufacturing quality. Approval decisions are made after extensive assessment.

3.1.2. Preclinical and Clinical Validation Requirements

Pharmaceutical companies must file a safety report that outlines the overall safety findings, emphasizing the identified risks and benefits of the drug before approval is given to proceed with clinical trials. The safety report should encompass an overview and summary, risk assessment, preclinical safety data, clinical safety data (human studies), pharmacovigilance plans, known and potential risks, immunogenicity (for biologics), special population considerations, comparative studies, investigational new drug (IND) safety reporting, integrated summaries of safety (ISS), statistical analyses of safety data, and conclusions [56,57].

3.2. Challenges of In Silico Validation

The FDA must provide clear guidance on how computational models will be developed, validated, and documented. Standardized methodologies and criteria must be established for various applications, e.g., drug development, medical devices. The FDA has already begun to accept certain types of computational models, e.g., in silico clinical trials or modeling in pharmacokinetics [58]. Expanding this acceptance would require case studies and examples that show the effectiveness of computational data.

Computational models must be well-documented and made available so that independent parties, including the FDA, can replicate and validate the data. Transparency about the algorithms, data inputs, and assumptions used in the model is essential. The FDA must trust that computational models are unbiased and not subject to proprietary, unverified methods [59].

The FDA must assess the risk–benefit ratio before accepting computational in silico to in vivo validation data. The FDA may be more cautious about accepting computational data in high-risk areas, e.g., the safety of new drugs or devices [54]. It may be more open to receiving in silico to in vitro/in vivo validation data in lower-risk areas. The FDA sometimes uses a hybrid approach, combining computational data with experimental data before considering complete replacement.

3.2.1. Trustworthiness and Interpretability of AI Models

Ensuring the trustworthiness and interpretability of AI models in drug discovery is essential for regulatory approval, user adoption, ethical acceptance, and practical implementation. The increasing reliance on AI for drug development necessitates a comprehensive understanding of the fundamentals of machine learning and deep learning [60]. The European Union's strategy on trustworthy AI underscores the importance of collaboration among developers, stakeholders, policymakers, and domain experts in guiding AI applications in drug discovery [60]. To gain regulatory acceptance, AI models must be supported

by well-defined guidelines, harmonized frameworks, and effective policies that ensure safety, scalability, data privacy, governance, transparency, and equitable treatment [61].

Trustworthiness refers to an AI system's ability to consistently deliver accurate, unbiased, reproducible, and transparent outcomes. Reliable models should yield consistent predictions across similar conditions, with validation against multiple independent datasets. Clear documentation of data preprocessing, model training, hyperparameter tuning, and evaluation metrics is vital for building confidence in AI predictions.

AI models must be robust to variations in chemical structures, patient populations, and biological environments. Performance degradation can occur gradually or suddenly after a period of prolonged stability, underscoring the need for ongoing model monitoring [62]. Models should quantify uncertainty in their predictions to help users assess confidence levels and potential risks. Continuous retraining, periodic updating of data sources, and benchmarking against real-world data are essential to maintaining model relevance. Monitoring for concept drift ensures that AI models remain accurate over time.

Addressing bias is critical. Datasets used for training AI models must represent a diverse range of chemical scaffolds, patient demographics, and biological conditions to minimize biases that can affect predictions. Class imbalances in datasets can lead to the overrepresentation of certain groups or molecular features [63]. Incorporating diverse perspectives during data curation and employing systematic bias audits—such as scenario testing and stress testing—are necessary to identify and mitigate bias. Reducing bias is an ongoing process that requires continuous research and improvement.

Regulatory frameworks (e.g., the FDA, EMA) must be considered to ensure transparency in the development and deployment of AI models. Ethical concerns, including patient safety, data privacy, fairness, and accountability, must be systematically addressed. AI models should be designed to provide explanations for their predictions, facilitating trust among scientists and regulators. Explainable Artificial Intelligence (XAI) techniques, such as SHAP (SHapley Additive exPlanations) and LIME (Local Interpretable Model-Agnostic Explanations), enable the interpretation of complex models by highlighting feature contributions and local decision boundaries [64]. Such interpretability fosters transparency, supports regulatory compliance, and can reveal potential errors or biases, preventing downstream failures.

Developing robust, interpretable, and trustworthy AI models ensures that they can reliably support drug discovery pipelines while maintaining scientific rigor, regulatory compliance, and public trust [65].

3.2.2. Reproducibility and Reliability of Quantum-Enhanced Simulations

Reproducibility and reliability are pivotal for the acceptance and practical use of quantum-enhanced simulations in drug discovery. Quantum systems are sensitive to environmental noise, which can affect the consistency of results [66]. Current quantum hardware, known as Noisy Intermediate-Scale Quantum (NISQ) devices, exhibits noise-induced fluctuations that complicate reproducibility [67]. Additionally, differences in hardware implementations (e.g., superconducting qubits, trapped ions) contribute to variability across platforms [68]. Quantum algorithms themselves introduce probabilistic outcomes and quantum randomness, making exact replication of results challenging without advanced error correction.

To enhance reproducibility, benchmarking problems—such as small-molecule binding or basic quantum chemistry calculations—should be standardized across platforms, with comprehensive documentation of hardware configurations, quantum circuit parameters, and computational steps. Open-source frameworks, such as IBM's Qiskit, Google's Cirq, and Rigetti's Forest, can enhance transparency and consistency [68]. Implementing quan-

tum error mitigation techniques, including zero-noise extrapolation and readout error mitigation, can further improve the stability of results. Classical post-processing and validation routines complement quantum outputs by verifying the accuracy of the results.

Reliability refers to the confidence in the accuracy and robustness of simulation results. NISQ devices often have limited coherence times and high error rates, which can compromise the accuracy of simulation outcomes [69]. Quantum algorithms such as the Variational Quantum Eigensolver (VQE) and Quantum Monte Carlo methods are particularly susceptible to noise amplification [70]. Therefore, quantum predictions must be cross-validated against classical computational methods, such as density functional theory (DFT) and molecular dynamics simulations, as well as experimental data [55]. Hybrid quantum–classical workflows that integrate classical error correction loops and post-processing steps enhance the reliability of quantum-enhanced simulations.

Establishing frameworks to quantify uncertainty due to quantum noise—providing confidence intervals alongside results—will build trust in simulation outputs. Recent advances in quantum hardware, including increased qubit counts, improved coherence times, and lower error rates, are bringing practical applications closer to reality. Continued progress in quantum error correction, algorithm efficiency, and scalability is essential. Clear industry standards and regulatory guidelines will be necessary to ensure consistent and trustworthy applications of quantum-enhanced simulations in pharmaceutical research pipelines.

3.2.3. Data Biases and Ethical Considerations

Biases in data can compromise the performance and fairness of AI and quantum-driven models in drug discovery, potentially leading to inequitable or unsafe outcomes. Familiar sources of bias include clinical trial datasets that may disproportionately represent specific demographics, thereby limiting the model's applicability to diverse populations [71]. Historical data used for AI training can perpetuate existing healthcare disparities, such as gender- or ethnicity-based treatment inequalities [72]. Annotation biases—such as labeling errors in toxicity or disease classification—can also distort model predictions. Additionally, biased algorithm design can exacerbate existing data biases, notably if interpretability is lacking.

Ethical concerns encompass transparency, fairness, accountability, privacy, and the well-being of humans. The complexity of deep learning and quantum models often limits interpretability, reducing trust among regulators, clinicians, and patients [73]. Large datasets required for training pose significant challenges to privacy and data protection, particularly when involving sensitive patient information [74]. When AI or quantum models contribute to harmful outcomes—such as adverse drug reactions—accountability becomes complex, necessitating clear frameworks for determining responsibility among developers, regulators, and clinicians [75]. Automation may also displace roles traditionally held by laboratory personnel, with social and economic implications that must be managed.

Implementing secure data access, end-to-end encryption, and robust identity verification mechanisms is crucial for protecting patient data. Compliant cloud infrastructures and secure on-premises solutions can further enhance data privacy and security. Transparent explanations of AI and quantum predictions enable regulators and clinicians to assess risks and make informed decisions, improving trust and accountability.

Addressing biases and ethical considerations is essential to ensure that AI and quantum computing tools support equitable [76] and safe drug discovery processes. Continuous monitoring, rigorous validation, and adaptive frameworks are needed to maintain model fairness and transparency when comparing in silico versus in vivo data (Table 2).

Table 2. Comparing in silico quantum computational methods with in vivo live organization in a laboratory setting with live organisms.

Method	Quantum Calculation	Laboratory Validation	Comparison
Molecular Structure Prediction	Uses quantum computing methods (including quantum chemistry algorithms) to simulate the molecular structure, interactions, and stability of a potential drug candidate. This involves calculating properties, including bond lengths, angles, and molecular energy states.	Experimentally determines the molecular structure using methods such as X-ray crystallography or nuclear magnetic resonance (NMR) spectroscopy.	The calculated molecular structure (e.g., bond lengths, angles) is compared to the experimentally derived structure. Discrepancies may indicate areas where the quantum model needs refinement or where experimental conditions differ from theoretical assumptions.
Binding Affinity to Targets	Quantum refers to the study and prediction of how strongly a molecule (e.g., a drug or ligand) binds to its target, e.g., a protein, using quantum mechanics (QM) principles. By calculating the interactions at the electronic level, QM-based methods provide highly accurate insights into binding energetics and mechanisms, surpassing traditional approaches in procession.	Measures binding affinities experimentally using techniques such as surface plasmon resonance (SPR), isothermal titration calorimetry (ITC), or enzyme-linked assays.	Compare the predicted binding energies or disassociation constants from quantum calculations with the experimental results. A close match indicates that the quantum molecule accurately represents the molecular interactions.
Reaction Pathways and Mechanisms	It utilizes quantum computing to simulate the chemical reactions a drug may induce in the body, including metabolic pathways and interactions with enzymes. This provides insights into potential metabolites or degradation products.	Experimentally determines the reaction products or metabolites using techniques such as mass spectrometry (MS) or liquid chromatography (LC).	Check whether the reaction pathways and products predicted using quantum simulations align with experimental observations. This helps to validate whether the quantum model accurately predicts real biochemical reactions.
Thermodynamics in Kinetic Properties	Simulates thermodynamic properties, including free energy and entropy changes for reactions involving the drug, as well as kinetic parameters such as reaction rates and activation energy.	Experimentally measures thermodynamic properties using calorimetry or kinetic properties through reaction rate analysis (e.g., spectroscopic methods or chromatographic separation).	Compares the predicted thermal dynamic and kinetic values with those obtained from lab experiments. Deviations can help refine quantum models to include additional factors such as solvation effects or specific experimental conditions.

Table 2. *Cont.*

Method	Quantum Calculation	Laboratory Validation	Comparison
Solubility in Pharmacokinetics	Quantum solubility refers to the application of quantum mechanical (QM) principles to predict and understand the solubility of drug molecules in various solvents, a key parameter in pharmacokinetics (PK). Solubility impacts drug absorption, distribution, metabolism, and excretion (ADME) and influences a drug's bioavailability in terms of therapeutic efficacy.	Tests solubility experimentally and excess pharmacokinetics in vitro (e.g., cell-based assays) or in vitro (e.g., animal models).	Compare the predicted solubility, permeability, and metabolic stability with experimental data to validate the model's accuracy. If they match closely, the quantum predictions can be considered reliable for further development.
Toxicity Predictions	It utilizes quantum models to predict potential toxic interactions by simulating the interactions of the drug candidate with off-target proteins or DNA or by predicting potential toxic metabolites.	Conducts in vitro toxicity tests (e.g., using cell cultures) and in vivo toxicity studies in animal models to measure toxic effects.	Compare the predicted toxicity levels with laboratory findings. If the predictions align, this may help reduce reliance on extensive animal testing, as quantum molecules can be trusted for early-stage toxicity screenings.

3.2.4. Integration of Computational and Experimental Validation

Refining experimental assays through iterative feedback between computational predictions and experimental data enhances precision and minimizes the need for trial-and-error experimentation. Optimized experimental parameters, including concentration ranges, time points, and cell line selection, are guided by computational predictions [77]. AI-driven hypotheses, such as target identification and biomarker discovery, are validated using molecular biology techniques, including Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR), Ribonucleic Acid RNA sequencing (RNA-seq), and proteomics [78]. Similarly, quantum mechanical predictions of binding modes and reaction mechanisms are corroborated with structural biology methods such as X-ray crystallography, NMR spectroscopy, and cryo-electron microscopy [79]. This integrated workflow tailors experiments to specific biological systems or patient profiles prioritizes the most promising candidates and streamlines the drug development process by minimizing failed experiments.

Computational models, especially AI-driven ADMET predictions, enhance dosing strategies, identify potential safety concerns early, and refine experimental protocols, thereby significantly reducing the need for animal testing [80]. In vivo data on efficacy and toxicity outcomes are systematically fed back into these models, creating a self-improving cycle that accelerates hypothesis generation, testing, and refinement.

Regulatory standards, including those from the FDA and EMA, require rigorous validation, reproducibility, and transparent documentation of computational methods. Interdisciplinary collaboration among computational chemists, biologists, clinicians, quantum computing specialists, AI engineers, and regulators ensures the development of standardized and compliant workflows. Comprehensive documentation of computational

methodologies and validation procedures promotes reproducibility and facilitates regulatory acceptance.

Future research should focus on standardizing biological datasets, integrating multi-omics data, and developing explainable AI (XAI) models to enhance interpretability and trust [81]. Advances in quantum computing are expected to provide higher-fidelity simulations, narrowing the gap between computational predictions and experimental outcomes. Integrating computational models with automated laboratory experiments and robotics will further expedite the transition from in silico predictions to clinical validation, ultimately accelerating drug development and improving clinical success rates.

3.2.5. Standardizing AI and Quantum Model Validation

Standardization of AI and quantum model validation is essential for ensuring reliability, reproducibility, regulatory compliance, and industry-wide adoption. Clear standards build confidence among researchers, regulators, and industry partners by facilitating consistent benchmarking and comparability [82]. Harmonized interactions with regulatory bodies such as the FDA and EMA can be achieved by establishing open-access repositories for algorithms and quantum circuits, defining consistent performance metrics—such as accuracy, specificity, sensitivity, F1-score, and Area Under the Curve (AUC-ROC—and thoroughly documenting data sources, preprocessing methods, and quality assurance protocols [61,82].

For quantum models, standardized benchmarks should include energy calculation accuracy, binding affinity predictions, and quantification of quantum noise. The adoption of industry-wide benchmark datasets will further facilitate the evaluation of model performance. AI and quantum predictions should be validated through standardized in vitro assays, including binding assays, toxicity screens, and cell-based assays [83]. Acceptance thresholds for model predictions must be defined to align with experimental results, and protocols should be established for translating in silico predictions into animal experiments with clear endpoints (e.g., PK/PD, efficacy, safety).

Furthermore, AI models should be consistently integrated into clinical workflows for patient stratification, dosing optimization, and predictive biomarker identification. Clearly defined metrics for evaluating the impact of AI and quantum assistance on clinical prediction accuracy and outcomes will ensure robust performance and facilitate clinical integration. Cross-validation techniques should be employed to estimate model robustness and mitigate the risk of overfitting. Regulatory submissions should document AI and quantum modeling processes, validation methodologies, datasets, and outcomes in accordance with guidance from agencies such as the FDA's Good Machine Learning Practice (GMLP) and the EMA's AI validation guidelines [84].

4. Proposed Regulatory Framework for AI and Quantum Computing in Drug Discovery

4.1. AI Model Validation and Transparency

Robust validation of computational models against experimental data is essential to ensure predictive reliability. The FDA has issued draft guidance recommending that oral biopharmaceutical modeling approaches complement in vivo bioavailability and bioequivalence studies to support product quality and performance [22]. This guidance highlights the importance of developing accurate computational models that can reliably replace laboratory-generated data. Validation efforts must be collaborative, involving academia, industry, and regulatory agencies to establish reproducibility across diverse product types.

4.1.1. Explainable AI (XAI) Requirements for Regulatory Compliance

Standardized regulatory documentation is crucial for detailing AI methodologies, assumptions, limitations, and risk mitigation strategies. Compliance with guidelines, such as the FDA's GMLP and the EMA's AI validation guidance, requires thorough documentation of algorithm design, validation processes, and risk management frameworks. Explainable AI reports should provide clear explanations of model predictions and their underlying rationale, supported by human-in-the-loop (HITL) systems that integrate expert oversight at critical decision points. This approach maintains accountability and reinforces the importance of human expertise in AI-driven decision-making.

AI implementation must also align with ethical principles emphasizing fairness, transparency, accountability, and non-maleficence. Regulatory agencies, including the FDA, EMA, and ICH, have articulated expectations for transparency, reproducibility, auditability, and active risk management [85]. Human oversight remains integral to ensuring that AI augments—rather than replaces—expert judgment, supported by thorough and accessible documentation.

Compliance with laws such as the General Data Protection Regulation (GDPR) and the Health Insurance Portability and Accountability Act (HIPAA) requires transparent data governance. Techniques such as federated learning and differential privacy can help secure sensitive patient data [86]. Clear communication about data usage, storage, and protection enhances stakeholder trust, facilitating dialogue among regulators, healthcare professionals, and patients. Non-expert stakeholders also benefit from plain-language explanations of AI model outputs, limitations, and uncertainties.

4.1.2. Model Auditing and Documentation and Bias Assessment

Model auditing systematically evaluates AI and quantum models to ensure regulatory compliance, reliability, and ethical integrity. Audits should assess model accuracy, performance, and adherence to regulatory requirements while also evaluating transparency, explainability, and reproducibility [87]. Detailed documentation of datasets, including composition, provenance, limitations, and potential biases, helps identify and address issues related to data imbalance, algorithmic favoritism, and measurement inconsistencies.

Quantum drug discovery models, such as those utilizing the VQE or QML, necessitate specialized documentation, including quantum circuit design, parameter optimization, and hardware specifications. Audits should verify the security of encryption and incorporate robust cybersecurity measures to ensure the integrity of sensitive data. Given increasing regulatory expectations, standardized documentation frameworks—such as Model Cards and Datasheets—should be adopted. Continuous bias monitoring and proactive ethical assessments are crucial for the responsible deployment of AI and quantum models. Integrating these practices into model development processes fosters transparency, accountability, and continuous improvement.

4.2. Quantum Computing Guidelines

Quantum computing applications in drug discovery encompass molecular simulations (VQE/QPE), prediction of drug–target interactions, quantum-appropriate optimization (QAOA), and QML for large biological datasets [86,88]. Hardware variability—such as qubit counts, coherence times, and error rates—necessitates consistent benchmarking to ensure reproducibility.

Bias auditing is crucial in personalized drug development, necessitating equitable representation in training datasets and a rigorous evaluation of quantum model limitations. Transparent documentation of quantum architectures, gate sequences, measurement protocols, and training processes supports effective regulatory review. Integrating privacy-

preserving techniques, including federated learning and differential privacy, is crucial for safeguarding patient data [86].

Adherence to regulatory standards—including those from the FDA, EMA, and ICH—requires detailed documentation of quantum workflows and proactive engagement with regulators via pilot programs or regulatory sandboxes. These interactions enable early feedback, continuous compliance, and effective risk management.

Global harmonization efforts, such as the ICH's exploration of quantum computing validation guidelines and collaborations among the FDA, EMA, and MHRA, are still in the early stages. These agencies recognize the potential of quantum computing in molecular modeling, clinical trial optimization, and enhancing AI and machine learning (ML) capabilities [88]. Although no dedicated, harmonized guidelines currently exist, ongoing initiatives under digital health frameworks are expected to evolve in tandem with the maturation of quantum technology [89].

4.3. Ethical and Data Governance Considerations

Ethical frameworks must guide the integration of AI and quantum computing into pharmaceutical research to ensure fairness, accountability, and transparency. AI bias—stemming from unrepresentative training data—can compromise the efficacy and safety of drugs across populations, highlighting the importance of inclusive and diverse datasets. Explainability is crucial for securing regulatory approval and clinical trust, given the opaque nature of many AI and quantum algorithms. Ensuring that patients and clinicians understand the rationale behind AI-generated recommendations is crucial, supported by explicit and informed consent for the use of data.

The reuse of datasets for secondary predictions—while enabling insights into new indications—must be governed by robust data management practices to prevent misuse, such as the design of harmful compounds. Governance mechanisms should strike a balance between openness and security to mitigate risks while supporting scientific innovation. The question of ownership of AI- or quantum-discovered drugs remains complex, involving researchers, institutions, and technology developers. Quantum computing's capacity to accelerate molecular simulations adds further complexity to intellectual property considerations, requiring clear legal frameworks to manage novel methodologies and data dependencies [90].

5. Future Directions and Conclusions

5.1. Technological Advancements and Industry Adoption

Generative models, such as GANs, VAEs, and diffusion models, enable the design of novel, drug-like molecules from scratch. Tools like AlphaFold have transformed protein structure prediction, accelerating target identification. Large language models (LLMs) efficiently mine the biomedical literature and clinical trial data. AI systems integrate genomic, atomic, and clinical data to identify biomarkers and patient subtypes, as well as predict drug responses, thereby enhancing the selection of candidates for targeted therapies (Table 3).

Table 3. AI-driven drug discovery models.

AI-Model	Description of Model Function
DeepTox	It utilizes deep learning to predict toxicological endpoints, including mutagenicity, carcinogenicity, and organ toxicity. It analyzes molecular structures to identify potentially toxic properties.

Table 3. *Cont.*

AI-Model	Description of Model Function
Tox21 Challenge Models	Developed in collaboration with the NIH, EP, and FDA, these machine learning models predict drug toxicity by screening compounds for various toxicological effects, utilizing large datasets such as Tox21.
IBM Watson for Drug Discovery	Machine learning is used to predict adverse drug reactions and potential toxicity by analyzing extensive datasets, including chemical properties, biological activities, and clinical trials.
ADMET Predictor	From Simulations Plus, this software predicts absorption, distribution, metabolism, excretion, and toxicity (ADMET) properties, focusing on identifying any red flags in a compound's structure.
ToxCast	An EPA initiative, ToxCast, uses computational models and machine learning to assess chemical toxicity. It is beneficial for screening chemicals without extensive toxicology data.
Multi-Instance Multi-Label (MIML) Models	These are advanced machine learning models tailored to predict multiple toxicological endpoints simultaneously and are used by some drug development companies.

NIH, national institutes of health; EP: European parliament.

Active and reinforcement learning refine compound screening and lead optimization iteratively, while reinforcement learning models also assist in finding optimal synthesis routes and modifying chemical structures. Quantum computing offers more accurate simulations of molecular interactions, binding affinities, and reaction pathways compared to classical systems, addressing the challenges of modeling complex molecules. Hybrid algorithms, including Variational quantum eigensolver (VQE) and Quantum Approximate Optimization Algorithms (QAOAs), blend classical and quantum capabilities to deliver scalable solutions. Applications already include molecular energy estimation, which is crucial for understanding drug behavior.

QML combines quantum computing with AI to enhance learning and inference in high-dimensional molecular spaces, supporting tasks such as drug-enhanced feature selection and drug repurposing. Drug discovery platforms now incorporate end-to-end solutions that span from target discovery to candidate prediction, integrating digital twins, automated labs, and in silico trials.

The pharmaceutical industry is adapting documentation and validation strategies to meet regulatory expectations for AI- and quantum-derived drugs. This includes clear explanations of model outputs, ensuring traceability and addressing audit requirements. Although quantum hardware scalability remains a challenge, progress is ongoing. Standardization and validation of AI and hybrid models, which bridge the gap between computational predictions and laboratory results, remain critical areas of focus.

The integration of advanced technologies—including digital computing, AI, and quantum computing—has transformed drug discovery, approval processes, and innovation pipelines [91]. These technologies streamline drug development by enabling virtual screenings and digital models, thereby increasing the efficiency of the process. Enhanced predictive capabilities allow researchers to estimate drug toxicity and efficacy with improved precision, aligning with regulatory expectations. Collaborative frameworks, rigorous validation of computational methods, and technological advancements foster efficiency and open new opportunities for personalized and innovative therapies. Collectively, these advances promise to overcome longstanding limitations in drug development, contributing to a more effective and responsive pharmaceutical industry.

Bioinformatics tools now facilitate the large-scale prediction of protein structures, shifting the paradigm from traditional laboratory-based, hypothesis-driven approaches

to data-driven computational models. This transition enables a deeper understanding of drug interactions, toxicity, and efficacy at the molecular level [92]. The ability to simulate dynamic and complex systems is essential for elucidating how drugs interact with biological targets and behave within the human body [81].

5.1.1. Summary of Key Takeaways

Comparative validation between computational predictions and experimental results is crucial for ensuring the reliability of drug development. In silico validation involves computational simulations, such as molecular docking, pharmacokinetics, and toxicity assessments, to predict drug behavior. In vitro validation then tests these predictions in biological samples (e.g., cell cultures and enzymes), while in vivo studies in model organisms or clinical trials further confirm efficacy and safety. Quantum computing and AI technologies expedite the screening of large chemical libraries to identify promising candidates, accelerating timelines and reducing costs. AI alone enhances the accuracy and speed of candidate identification The integration of real-time data and predictive modeling is expected to become standard practice, given its impact on drug efficacy and safety [5]. Advances in virtual screening technologies increasingly leverage the convergence of AI and quantum computing [6], offering frameworks for integrating quantum algorithms with classical methods and accelerating drug discovery.

5.1.2. Recommendations for Researchers, Industry Stakeholders, and Policymakers

For Researchers

Incorporate ethical impact assessments, such as bias detection and fairness analysis, into the research design to ensure a thorough examination of potential ethical implications. Collaborate with ethics and legal experts to address the broader implications of drug discovery. Use high-quality, diverse, and representative datasets to avoid biased outcomes. Prioritize explainable AI (XAI) to enhance transparency and reproducibility and share datasets, models, and quantum simulation protocols under open-source licenses whenever feasible. Adhere to FAIR data principles and open-access publishing to foster collaboration. Develop interpretable hybrid AI–quantum frameworks and contribute to standardization efforts for the validation and benchmarking of quantum models.

For Industry Stakeholders

Establish ethical review boards within R and D teams and ensure compliance with data protection regulations (e.g., GDPR, HIPAA) in AI and quantum pipelines. Invest in cybersecurity measures to safeguard sensitive health and molecular data. Implement secure computing methods, including differential privacy and federated learning, to protect data integrity. Engage in pre-competitive collaborations to build shared AI and quantum platforms. Fund and support academic–industry partnerships that prioritize ethical and explainable innovation. Provide ongoing training in AI ethics, quantum computing, and regulatory knowledge and promote interdisciplinary talent development through joint university programs.

For Policymakers and Regulators

Develop risk-based, proportional regulations tailored to AI- and quantum-enabled drug discovery tools. Promote regulatory sandboxes to test innovative approaches before market authorization is granted [93]. Support initiatives that ensure global access to AI and quantum computing resources for the advancement of drug discovery. Mandate the inclusion of underrepresented populations in datasets used for drug development and research. Collaborate internationally to establish shared standards for validation, data governance, and ethical compliance. Define clear regulatory expectations for quantum–

classical hybrid models. Fund public AI and quantum research centers and open-access data repositories and provide grants and incentives for projects aligned with public health priorities and responsible innovation [94].

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