Advances in Drug Discovery and Development in the Pharmaceutical Industry: Innovative Strategies, High-Throughput Screening, and Translational Approaches for Accelerated Therapeutic Development

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Article Info

ISSN (online): 3049-0421
Volume: 02
Issue: 06
November-December 2025
Received: 18-09-2025
Accepted: 16-10-2025
Published: 14-11-2025
Page No: 44-50

Abstract
The discovery and development of novel therapeutic agents constitute one of the most intellectually demanding and resource-intensive endeavours in modern biomedical science. The average timeline from initial target identification to regulatory approval spans more than a decade, with associated costs frequently exceeding two billion US dollars per successfully approved drug [1, 2]. High attrition rates, particularly at late-stage clinical development, continue to challenge the pharmaceutical industry and underscore the urgent need for innovation across the drug development continuum. This article critically examines recent advances in pharmaceutical research and development, with particular emphasis on emerging strategies in target identification and validation, high-throughput screening, lead optimization, and translational methodologies. Key methodological advancements discussed include genomic and proteomic approaches to target discovery, miniaturized screening platforms, artificial intelligence-assisted compound design, patient-derived preclinical models, and adaptive clinical trial architectures. The integration of biomarker-driven patient stratification with precision medicine frameworks has demonstrated particular promise in improving both the efficiency and therapeutic relevance of drug development programs. Regulatory innovations, including accelerated approval pathways and modular development frameworks, are also evaluated in the context of global harmonization challenges. Collectively, these advances represent a paradigm shift towards more efficient, scientifically rigorous, and patient-centric pharmaceutical development. The article concludes by identifying critical future directions, including the expanded application of generative artificial intelligence, real-world evidence integration, and equitable global access frameworks, as defining priorities for the next era of pharmaceutical innovation.

Keywords: Drug discovery, Pharmaceutical development, Translational research, High-throughput screening, Lead optimization, Precision medicine

1. Introduction

Pharmaceutical drug discovery and development represents an extraordinarily complex undertaking that demands the convergence of multiple scientific disciplines, including molecular biology, medicinal chemistry, pharmacology, clinical medicine, and regulatory science. Despite decades of scientific progress and unprecedented investment, the productivity of the pharmaceutical industry has not kept pace with escalating research and development expenditures [1]. The attrition problem, whereby the overwhelming majority of candidate molecules fail before reaching patients, is particularly acute in therapeutic

areas such as oncology, central nervous system disorders, and antimicrobial resistance, where unmet clinical need is greatest [2, 3].

Historically, drug discovery proceeded through largely empirical, hypothesis-driven processes characterized by low throughput, limited mechanistic insight, and prolonged development timelines. The advent of combinatorial chemistry and early high-throughput screening technologies in the 1990s represented the first systematic attempt to industrialize drug discovery, although initial expectations for transformative productivity gains were not fully realized [4]. Subsequent decades have witnessed a more nuanced evolution, characterized by the integration of structural biology, bioinformatics, and translational science to generate more physiologically relevant and mechanistically informed drug candidates [5].

Contemporary pharmaceutical research is increasingly shaped by the convergence of technological innovation and scientific reconceptualization. The development of CRISPR-based genomic tools, advanced proteomic platforms, organ-on-chip models, and deep learning architectures has collectively transformed both target biology and candidate optimization [6]. These advances are occurring in parallel with important changes in the regulatory landscape, including the adoption of adaptive clinical trial designs, biomarker-driven approvals, and accelerated development pathways for breakthrough therapies. The present article provides a comprehensive review of these developments, critically examining their scientific foundations, translational implications, and the challenges that remain to be resolved.

2. Modern Approaches in Target Identification and Validation

2.1. Molecular and Genomic Strategies

The identification of biologically valid and clinically relevant therapeutic targets constitutes a foundational determinant of drug development success. Traditional approaches relying on established target classes, such as G-protein-coupled receptors, kinases, and nuclear receptors, have yielded important therapies but have also contributed to the concentration of the pharmaceutical pipeline around a relatively small set of well-characterized mechanisms [7]. The completion of the human genome project, and the subsequent development of next-generation sequencing platforms, opened expansive new opportunities for target discovery grounded in the functional genetics of human disease [8].

Genome-wide association studies have identified thousands of loci associated with complex diseases, while Mendelian randomization analyses have provided causal inference regarding potential therapeutic targets from human genetic data [3]. Critically, targets supported by human genetic evidence have been shown to exhibit substantially higher success rates in clinical development, underscoring the translational value of genetic validation strategies [9]. Functional genomic screens employing CRISPR-Cas9 libraries now enable systematic interrogation of gene essentiality across diverse disease models, providing unprecedented resolution in the identification of novel vulnerabilities in cancer, infectious disease, and rare genetic disorders [10].

2.2. Proteomics, Biomarkers, and Precision Medicine Integration

Advances in mass spectrometry-based proteomics have substantially enriched target validation workflows by enabling the quantitative characterisation of protein expression, post-translational modification states, and protein-protein interaction networks at a systems level [11]. Integration of proteomic data with transcriptomic and metabolomic profiles facilitates multi-omic target prioritization, allowing researchers to identify molecular nodes of greatest therapeutic relevance within complex biological networks. This systems biology approach has proven particularly valuable in oncology, where tumour heterogeneity and network rewiring frequently undermine single-target therapeutic strategies [12].

The precision medicine framework, which seeks to match therapeutic interventions to defined molecular or genetic patient subgroups, has fundamentally altered the conceptualization of target validation. Rather than seeking targets operative across broad patient populations, contemporary development programs increasingly aim to define biomarker-selected populations in which target engagement is most likely to translate into clinical benefit [13]. The co-development of companion diagnostics alongside lead therapeutic programs has become both a scientific imperative and, in many regulatory contexts, a regulatory requirement, particularly for oncology and rare disease indications [14].

3. High-Throughput Screening and Lead Optimization

3.1. Screening Technologies and Assay Development

High-throughput screening constitutes a cornerstone of contemporary pharmaceutical drug discovery, providing the technical infrastructure necessary for the systematic interrogation of large compound libraries against defined molecular targets or cellular phenotypes [5]. Modern HTS platforms employ miniaturized assay formats in 384-well and 1536-well microplate configurations, supported by robotic liquid handling systems, automated compound management, and sophisticated data acquisition infrastructure. Ultra-high-throughput screening capabilities now permit the interrogation of compound libraries comprising several million entries within operationally feasible timeframes, substantially expanding the chemical space accessible for early discovery [15].

Assay development for HTS demands rigorous optimization of biochemical or cell-based systems to ensure selectivity, sensitivity, and signal stability at miniaturized scales. Cell-based phenotypic screens, which assess compound effects on complex cellular behaviours rather than isolated molecular targets, have experienced renewed interest as a complementary strategy to target-based approaches, particularly in disease areas where target biology remains incompletely understood [16]. The development of high-content imaging platforms has further enriched phenotypic screening by enabling quantitative, multi-parametric analysis of cellular morphology, viability, and functional endpoints in response to compound treatment, yielding mechanistically informative hit profiles [6].

3.2. Lead Identification, Structure-Activity Relationships, and Optimization

The progression from primary screening hits to optimized lead candidates requires systematic application of medicinal chemistry principles and pharmacological profiling. Hit confirmation and counter-screen strategies are essential initial steps, designed to eliminate artefacts, pan-assay interference compounds, and assay-specific false positives before committing to resource-intensive optimization campaigns [7]. Confirmed hits are subsequently subjected to structure-activity relationship analyses, wherein systematic chemical modifications are evaluated to delineate the molecular features governing potency, selectivity, and physicochemical properties.

Contemporary lead optimization is fundamentally data-driven, relying on integrated computational and experimental workflows to navigate complex multi-parameter optimization landscapes. Quantitative structure-activity relationship models, pharmacophore mapping, and three-dimensional structural data from X-ray crystallography or cryo-electron microscopy provide the mechanistic foundation for hypothesis-driven compound design [8]. ADMET profiling, encompassing the assessment of absorption, distribution, metabolism, excretion, and toxicity characteristics, is now integrated throughout the optimization process rather than deferred to late-stage preclinical evaluation, enabling the early elimination of candidates with unfavourable pharmacokinetic or safety liabilities [17].

4. Preclinical and Translational Strategies

4.1. Advanced Experimental Models

The translation of promising drug candidates from laboratory discovery programs to clinical evaluation remains one of the most significant challenges in pharmaceutical development, with high attrition at the preclinical-clinical interface attributable in substantial part to the limited predictive validity of conventional experimental models [9]. Standard two-dimensional cell culture systems and inbred rodent models, while indispensable experimental tools, frequently fail to recapitulate the complexity of human disease physiology or the pharmacokinetic and pharmacodynamic behaviour of candidate compounds in human subjects [18]. Recognition of these limitations has driven substantial innovation in preclinical model development.

Three-dimensional organoid systems, derived from patient tissue or induced pluripotent stem cells, now provide physiologically relevant, genetically defined models of diverse human tissues and disease states [19]. Organ-on-chip microphysiological systems, which integrate living human cells within microfluidic architectures that recapitulate organ-level function, offer additional dimensions of physiological fidelity, including fluid flow, mechanical stimulation, and multi-organ interaction [10]. Patient-derived xenograft models, in which human tumour fragments are engrafted into immunocompromised murine hosts, have substantially improved the predictive relevance of oncology preclinical studies by preserving intratumoural heterogeneity and histopathological characteristics representative of the clinical disease [20].

4.2. Translational Bridging and Regulatory Interfaces

Effective translation from preclinical findings to clinical development requires rigorous application of translational pharmacology principles, including the establishment of quantitative pharmacokinetic-pharmacodynamic relationships that inform dose selection and therapeutic index assessment for first-in-human studies [21]. Physiologically based pharmacokinetic modelling has become an integral component of the translational toolbox, enabling mechanistic prediction of drug behaviour across species and supporting regulatory submissions with quantitative scientific rationales for clinical dose selection [11].

The integration of biomarker strategies across the preclinical-clinical boundary represents a critical translational priority. Preclinical biomarker qualification, establishing the relationship between candidate biomarkers and pharmacodynamic endpoints or disease progression markers, provides the scientific foundation for their subsequent deployment in clinical trials as pharmacodynamic, predictive, or prognostic tools [22]. Regulatory agencies, including the US Food and Drug Administration and the European Medicines Agency, have established formal biomarker qualification programs to facilitate the systematic development and cross-program utilization of validated biomarkers, providing important infrastructure for translational medicine at the ecosystem level [14].

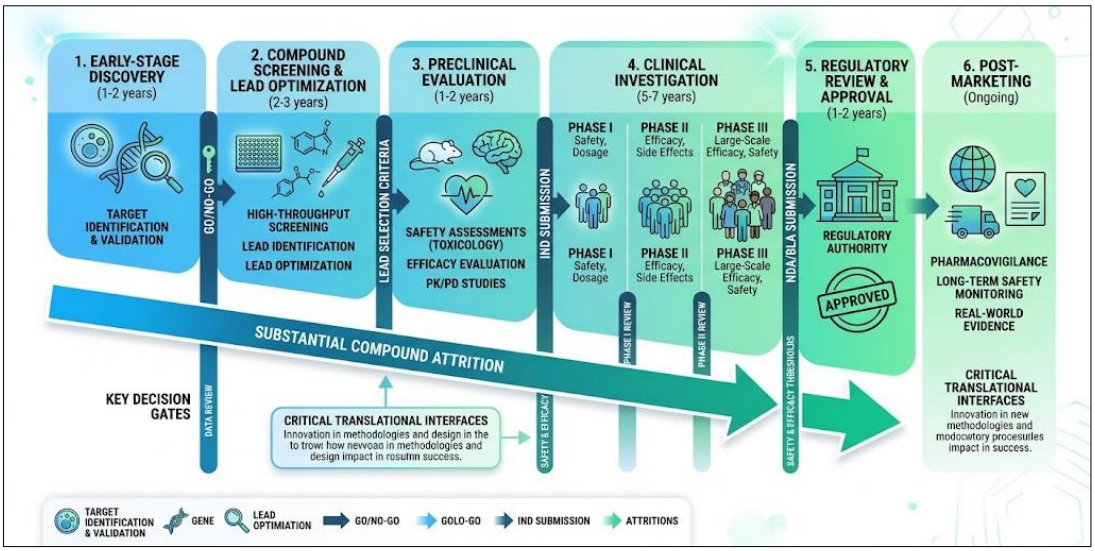

Fig 1: Overview of the drug discovery and development pipeline

5. Clinical Development Innovations

5.1. Adaptive Trial Design and Biomarker-Guided Approaches

The design of clinical trials has undergone substantial evolution in response to recognition that traditional fixed-design randomized controlled trials, while methodologically rigorous, impose significant inefficiencies that contribute to the high cost and prolonged timelines of pharmaceutical development [12]. Adaptive clinical trial designs incorporate pre-specified rules for modifying trial parameters, such as sample size, dose allocation, or patient population criteria, based on accumulating data from within the trial itself, enabling real-time optimization of trial conduct without compromising statistical integrity [23].

Bayesian adaptive designs, seamless Phase II/III protocols, and master protocol frameworks, including basket trials and umbrella trials, have demonstrated particular utility in oncology, where tumour molecular heterogeneity necessitates flexible approaches to patient stratification and endpoint selection [24]. Basket trials evaluate a single targeted therapy across multiple tumour types sharing a common genetic alteration, while umbrella trials assess multiple targeted therapies within a single tumour histology stratified by molecular subtype. These approaches have accelerated the development of precision oncology agents while providing mechanistically coherent evidence regarding the relationship between genomic biomarkers and therapeutic response [13].

5.2. Decentralized Trials and Patient-Centric Development

The conceptualization of clinical trials as geographically distributed, patient-centric investigations, rather than site-centric research exercises, has gained substantial momentum, accelerated by the operational imperatives imposed by the COVID-19 pandemic [25]. Decentralized clinical trial elements, including remote electronic consent processes, home-based clinical assessments, telemedicine visits, direct-to-patient investigational product delivery, and wearable biosensor data capture, collectively reduce participant burden, broaden geographic and demographic access, and potentially enhance data quality through increased assessment frequency in naturalistic settings [15].

6. Technological and Computational Enhancements

6.1. Artificial Intelligence in Target Prediction and Molecular Design

The application of artificial intelligence and machine learning to pharmaceutical drug discovery has moved from exploratory academic research to operational deployment within major industrial pipelines over the course of the past decade [16]. Deep learning architectures, including convolutional neural networks, graph neural networks, and transformer-based language models, have demonstrated remarkable capability in predicting protein structure, molecular bioactivity, ADMET properties, and drug-target interaction profiles from large experimental datasets [26]. The landmark release of AlphaFold2 by DeepMind and its subsequent expansion to encompass the near-complete human proteome has fundamentally transformed structure-based drug design by providing high-confidence three-dimensional structural predictions for proteins previously inaccessible to experimental crystallographic or cryo-electron microscopy determination [27].

Generative AI models, including variational autoencoders, generative adversarial networks, and diffusion model architectures, now enable the de novo design of molecular structures with defined target engagement and pharmacokinetic property profiles, effectively expanding the explorable chemical space beyond the boundaries of existing compound libraries [17]. These technologies are increasingly integrated into multi-objective optimization workflows that simultaneously optimize potency, selectivity, synthetic accessibility, and ADMET characteristics, enabling the more efficient identification of candidate molecules with balanced therapeutic profiles [28].

6.2. Computational Integration Across the Development Continuum

Beyond molecular design, computational approaches are being deployed across the full drug development continuum. Physiologically based pharmacokinetic-pharmacodynamic models support translational dose prediction and clinical trial simulation, while in silico toxicity prediction platforms integrate structural alerts, machine learning classifiers, and mechanistic toxicological models to support early safety assessment [18]. The integration of electronic health records, real-world evidence databases, and genomic biobanks with computational analytics platforms is creating new opportunities for retrospective target identification, comparative effectiveness research, and post-approval safety surveillance [29].

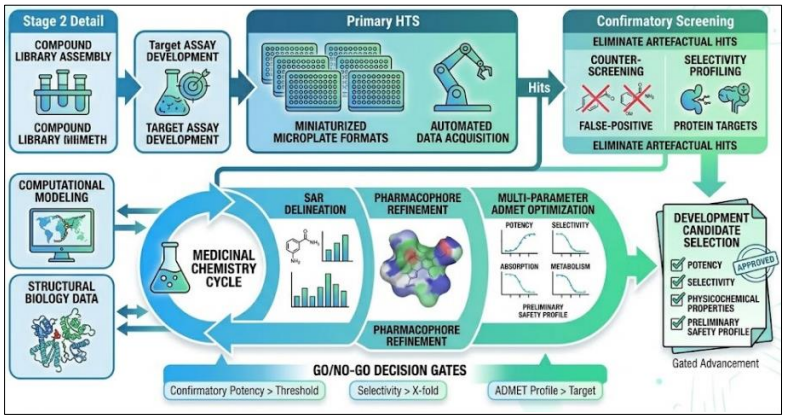

Fig 2: Workflow of high-throughput screening and lead optimization

7. Challenges, Ethical, and Regulatory Considerations

7.1. Regulatory Frameworks and Global Harmonization

The regulatory environment governing pharmaceutical drug development has evolved considerably in response to scientific advances, public health imperatives, and post-market safety experiences, but significant challenges related to global harmonization, adaptive framework design, and the regulation of novel modality therapies remain [19]. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use has produced influential guidance documents covering quality, safety, and efficacy domains, providing a foundation for regulatory alignment across major jurisdictions including the United States, European Union, Japan, and increasingly, emerging market regulatory agencies [30]. Nevertheless, meaningful differences in regulatory requirements, evidentiary standards for approval, and post-market obligation frameworks persist, imposing additional development costs and delays for globally marketed products [24].

The emergence of novel therapeutic modalities, including gene therapies, RNA therapeutics, cell-based medicines, and bispecific antibody constructs, has created substantial regulatory science challenges, as conventional preclinical and clinical development frameworks are not always readily applicable to these mechanistically distinct interventional approaches [25]. Regulatory agencies in major jurisdictions have introduced specialized designation pathways, including the FDA Regenerative Medicine Advanced Therapy designation and the EMA PRIME scheme, to facilitate the development of transformative therapies for serious conditions, providing early scientific engagement and rolling review opportunities for qualifying programs [31].

7.2. Ethical Considerations and Global Access

Ethical considerations permeate every stage of pharmaceutical drug development, from the design of preclinical experiments and first-in-human dose escalation studies to the implementation of patient consent processes, management of incidental genomic findings, and equitable access to beneficial therapies following approval [20]. The increasing application of patient genomic data in drug development programs raises important questions regarding data governance, secondary use consent, and the equitable sharing of benefits derived from biobank research, particularly where donor populations are drawn from economically disadvantaged communities [32].

The global access challenge remains among the most ethically significant issues in pharmaceutical development, as the majority of novel therapeutics are initially developed for and accessible to high-income country populations, with substantial delays in access and affordability for low- and middle-income country populations bearing disproportionate burdens of preventable disease [33]. The COVID-19 pandemic exposed the fragility of global pharmaceutical supply chains and the inadequacy of existing mechanisms for equitable vaccine and therapeutic distribution, catalysing renewed policy attention to tiered pricing, technology transfer, voluntary licensing arrangements, and investment in local manufacturing capacity as components of a more equitable global medicines ecosystem [21].

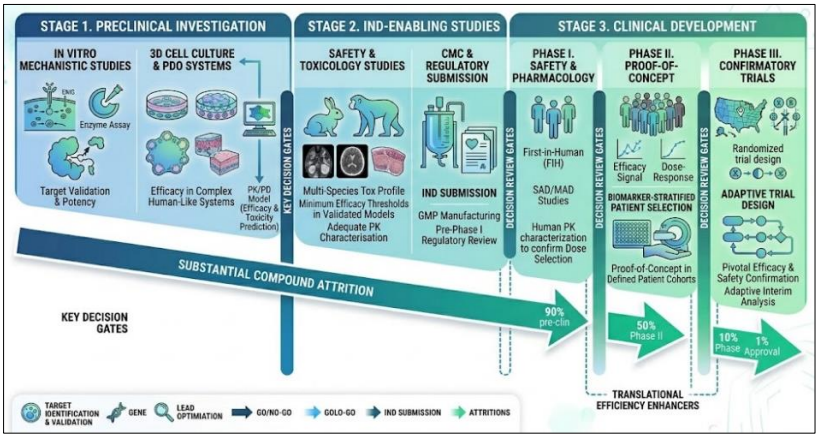

Fig 3: Translational pathway from preclinical investigation to clinical development

8. Conclusion

Pharmaceutical drug discovery and development stands at a pivotal juncture, defined by the convergence of transformative scientific capabilities and an evolving understanding of the biological complexity that underlies human disease. The integration of genomic target validation, high-throughput screening, AI-assisted molecular design, advanced translational models, and adaptive clinical methodologies represents a coherent and mutually reinforcing framework for substantially improving the efficiency and success rates of pharmaceutical development programs [34, 35]. The translation of these innovations into systematic productivity gains across the pharmaceutical pipeline requires not only scientific advancement but also the deliberate alignment of organisational incentives, regulatory frameworks, and data infrastructure to support more collaborative and data-intensive approaches to drug development.

Future directions of particular scientific significance include the expanded application of generative AI architectures to multi-target molecular design, the integration of single-cell multi-omic profiling into target validation and clinical biomarker programs, and the development of microphysiological system platforms with sufficient complexity and validated relevance to support regulatory-grade safety and efficacy assessment [36]. The equitable integration of diverse patient populations into drug development programs, both to ensure the representativeness of clinical evidence and to address the global burden of undertreated diseases, constitutes an ethical and scientific imperative that must be prioritized alongside technological innovation [37].

Ultimately, the realization of the full potential of contemporary pharmaceutical innovation will depend on the sustained commitment of the scientific, industrial, clinical, and regulatory communities to collaborative, evidence-driven, and patient-centric approaches to therapeutic development. The advances reviewed in this article collectively represent a promising trajectory, but their translation into improved therapeutic outcomes for patients worldwide demands continued scientific rigor, methodological innovation, and a commitment to the equitable distribution of the benefits of pharmaceutical progress [38].

Table 1: Comparison of Conventional versus Modern Drug Discovery Strategies

Parameter	Conventional Strategy	Modern Strategy	Impact on Drug Development
Target Identification	Phenotypic screening; largely empirical; limited mechanistic rationale	Genomics, proteomics, transcriptomics; systems biology; CRISPR-based functional screens [3, 4]	Markedly improved target specificity; reduced attrition in later development phases
Screening Technology	Low-throughput biochemical assays; manual compound testing; days per compound	HTS and uHTS platforms; miniaturized 1536-well formats; automated liquid handling [5, 6]	Screening of millions of compounds in days; substantially increased hit rates
Lead Optimization	Iterative medicinal chemistry with limited computational guidance; slow SAR cycles	AI-driven QSAR modelling; fragment-based design; ADMET prediction platforms [7, 8]	Accelerated optimization timelines; improved pharmacokinetic and safety profiles
Preclinical Models	Standard rodent models; limited translational relevance; high interspecies variability	Patient-derived organoids; microphysiological systems; 3D bioprinted tissues [9, 10]	Enhanced predictive validity; reduced reliance on animal experimentation
Clinical Trial Design	Fixed-dose, parallel group, one-size-fits-all design; high failure rates	Adaptive designs; basket and umbrella trials; real-world evidence integration [11, 12]	Greater flexibility; faster go/no-go decisions; reduced patient exposure to ineffective therapies
Development Cost	Estimated USD 2.6 billion per approved drug; high attrition at late phases	Computational front-loading; biomarker enrichment; modular regulatory pathways [13, 14]	Potential 30-50% cost reduction through earlier attrition and precision patient selection
Success Rate	Approximately 10% from Phase I to approval; low for oncology and CNS indications	Biomarker-stratified populations; companion diagnostics; genotype-phenotype matching [15]	Emerging evidence of improved Phase II-to-III transition rates in biomarker-selected trials

Table 2: Advantages, Limitations, and Recent Innovations in Preclinical and Clinical Development

Domain	Advantages	Limitations	Recent Innovations
Preclinical *in vitro* Models	Cost-effective; mechanistically controllable; high reproducibility in 2D culture	Poor recapitulation of *in vivo* physiology; limited predictive power for complex diseases	3D spheroids, patient-derived organoids, and organ-on-chip systems with real-time biosensing [9, 16]
Animal Models	Whole-organism pharmacology; regulatory acceptance; safety signal detection	Significant interspecies differences; ethical concerns; poor CNS and immuno-oncology translation	Humanized mouse models; xenograft-PDX systems; zebrafish models for toxicity screening [17, 18]
Adaptive Clinical Trials	Flexible dosing and population enrichment; faster decision-making; ethical efficiency	Statistical complexity; risk of type I error inflation; intensive data infrastructure requirements	Bayesian adaptive designs; seamless Phase II/III protocols; master protocol frameworks [11, 19]
Biomarker-Guided Development	Patient stratification; enhanced signal detection; companion diagnostic integration	Biomarker validation burden; regulatory co-development complexity; reduced generalizability	Liquid biopsy platforms; multi-omic biomarker panels; real-world evidence biomarker validation [20, 21]
Computational and AI Tools	Accelerated virtual screening; multi-parameter optimization; de novo molecular design	Training data quality dependence; interpretability challenges; regulatory uncertainty for AI outputs	AlphaFold-informed structure-based design; generative AI for scaffold generation; federated learning [22, 23]
Regulatory Pathways	Accelerated approval; breakthrough designation; rolling review for urgent needs	Post-approval study obligations; confirmatory trial delays; inconsistent global harmonization	ICH Q12 lifecycle management; FDA RMAT designation; EMA PRIME scheme for advanced therapies [24, 25]

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