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Review

Evolution of Drug Development and Regulatory Affairs: The Demonstrated Power of Artificial Intelligence

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ABSTRACT

Purpose: Artificial intelligence (AI) refers to technology capable of mimicking human cognitive functions and has important applications across all sectors and industries, including drug development. This has considerable implications for the regulation of drug development processes, as it is expected to transform both the way drugs are brought to market and the systems through which this process is controlled. There is currently insufficient evidence in published literature of the real-world applications of AI. Therefore, this narrative review investigated, collated, and elucidated the applications of AI in drug development and its regulatory processes.

Methods: A narrative review was conducted to ascertain the role of AI in streamlining drug development and regulatory processes.

Findings: The findings of this review revealed that machine learning or deep learning, natural language processing, and robotic process automation were favored applications of AI. Each of them had considerable implications on the operations they were intended to support. Overall, the AI tools facilitated access and provided manageability of information for decision-making across the drug development lifecycle. However, the findings also indicate that additional work is required by regulatory authorities to set out appropriate guidance on applications of the technology, which has critical implications for safety, regulatory process workflow and product development costs.

Implications: AI has adequately proven its utility in drug development, prompting further investigations into the translational value of its utility based on cost and time saved for the delivery of essential drugs.

Introduction

The current drug development landscape is plagued by costly, time-intensive processes that often yield suboptimal results.[1] Artificial intelligence (AI) has been suggested as a potential solution for the challenges faced in drug development. Expectations for AI in this field are high; thus, for pragmatic utilization of this technology, it is necessary to investigate its applicability in drug development and regulatory processes. This is particularly important for the current era of computational technology in drug development, which seeks to capitalize on large and increasingly complex data to guide development outputs.[2] The definition of AI typically varies within the literature; however, for the purpose of this review, AI is defined as a scope of technology that is capable of mimicking human cognitive functions, such as problem-solving, pattern recognition and learning.[3] This technology is closely linked to Big Data, which refers to expansive and complex collections of data that cannot be effectively processed using traditional data analysis tools.[4,5] Big Data, as it pertains to drug development, can be derived from a variety of sources, which include but are not limited to electronic health records (EHR), insurance claims, administrative data, and data derived from high-throughput screening in drug modeling. The convergence of AI, Big Data, and drug development occurs in each stage of the developmental lifecycle of a drug. Within these stages, AI technologies have been proposed as being capable of improving the efficiency of drug development by managing designs, computations, and forecasts more effectively in comparison to existing methods.[6] The potential benefits of this are significant, holding great value in drug development as the current drug development landscape can cost drug sponsors over 2 billion

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United States (US) dollars to bring a single drug to the market.[1] Considering this, it is important to understand how the most recent applications of AI are evolving to optimize the drug development process.

The Inefficiencies of Drug Development

To understand the value of AI in drug development, it is necessary to first elucidate the problems that result in high costs and contextualize how AI-driven advancements are intended to enhance the efficiency of development systems. Eroom's Law, coined by Jack Scannell, represents the observation that despite technological advancements between 1960 and 2010, drug development has progressively become slower and more expensive.[7] In contrast, Moore's Law describes how technologies improve with time, becoming more efficient and less expensive in the process. This has not been noted in drug development, despite breakthrough developments such as high-throughput screening and computational drug design, among others.[8] Currently, significant advancements within drug development have resulted in high volume and high output processes. However, according to the literature reviewed in this paper, these advancements have often been described as superficial, with the consensus that productivity from basic research to regulatory authorization has declined.[9] While such advancements have facilitated the identification of additional drug targets and drug-like molecules and improved filtering capacities, the likelihood that small molecules become fully approved drugs has remained fairly constant over the past 5 decades while research and development (R&D) processes have become less efficient and more expensive.[7] The complexities associated with drug development are broad and often nuanced based on the type of drug in development, as exemplified by the findings on the limitations of developing drugs for cardiovascular and nervous system disorders.[8,10] The issues highlighted in this review are a summative observation of key themes detailed in the limitations of drug development as described by Scannell et al[2] and Tormay.[11]

"Better than the Beatles" Problem and "The low-hanging fruit" Problem

The "Better than the Beatles" problem describes the idea of the improbability of developing a new drug that is better than existing approved drugs for specific targets, as every drug that is released into the market raises the stakes for efficacy, making it increasingly difficult for subsequent drugs to meet the rising standards.[7] The "low-hanging fruit" problem posits that drug targets that are easy to obtain have already been identified, and drugs have been developed for those targets. As a result, more complex targets remain, requiring more extensive investment of money and time in the R&D process. This notion aligns with the understanding that the attrition rate for compounds with novel mechanisms is higher than those with known mechanisms.[11] This problem has potential to overlap with the first, as this has been noted in the development pipeline for cardiovascular drugs wherein clinical trials are larger at baseline than those of other therapeutic areas.[8]

"Throw money at it" Tendency and "Basic-research-brute-force" Bias

The "Throw money at it" tendency describes a phenomenon where drug R&D sponsors allocate greater human capital and additional resources with the expectation that this will increase return on investment by being the first to market a particular drug.[7] The "Basic-research-brute-force" bias refers to the tendency to overestimate the value of advances in basic research, particularly the identification and validation of drug targets in the preclinical stages driven by molecular reductionism.[7] Such advancements are intended to produce better biological and chemical therapeutic developments with greater reproducibility and reliability at lower costs.[12] However, there is an evident gap in resource inputs and biomedical research outcomes which produce marketable drugs, a direct failure of the approach to counter attrition by pushing a greater number of projects into the development pipeline.[13,14] Both of these issues relate strongly to the translational value of current drug development approaches, from laboratory bench to patient, which is limited even in advanced markets such as those in Europe and the US.[9]

"Cautious regulator" Problem

The "Cautious regulator problem" describes the rising stringency in the regulation of drugs that are released into the market owing to the failures and threats posed by previously released drugs. Although this is crucial for public safety, it substantially increases the cost of developing new drugs as regulations become more challenging to meet.[7] Furthermore, when examining the clinical stages of drug development, 4 challenges contribute to a decrease in the efficiency of the processes. Firstly, the "narrow clinical search" problem arises from a change in approach, shifting from a broader search for therapeutic potential in biologically active agents to an approach that favors precise effects from molecules designed with a single drug target in mind. Second is the "big clinical trial" problem, which refers to clinical trials that are designed as large and costly experiments that attempt to replicate the sterile and controlled environments of an experiment using human subjects. These trials are often multi-centred, producing heterogeneous results, and can be expensive. The third challenge is the "multiple clinical trial" problem, an extension of the "better than the Beatles" and "cautious regulator" problems. It speaks to the strictness of medical practice, where regulators are less likely to accept generalizations on drug efficacy across heterogeneous patient groups, leading to fewer indications associated with drugs and more clinical trials per drug to prove efficacy in varied indications. Lastly, the "long cycle time" problem describes the current time investment required for clinical trials.[7]

Regulatory and compliance needs associated with all therapies are interwoven into the drug development process. The pharmaceutical regulatory industry combines legal, administrative, and technical measures undertaken by government and drug sponsors to guarantee the safety, efficacy, and quality of therapies.[15] Similar to the R&D and clinical stages of drug development, the regulatory industry must overcome several considerations and obstacles with the intention of delivering safe and efficacious drugs to the market. This includes issues such as the role of public engagement in regulatory science, data ownership, and control, the pre-competitive space, as well as aspects of regulatory science like biomarkers, clinical trial data integration, modeling, and surveillance.[16] Furthermore, regulatory professionals today are currently positioned in a way that is often limiting to their scope of work.[17] Many of these professionals focus on specific subprocesses without understanding or being exposed to the full scope of product development. Furthermore, these subprocesses they are involved in, are often time-intensive and performed manually in a siloed approach.[17,18] Moving forward, these professionals will need to focus on value-added outputs that speak directly to patient needs.[17] An example of this would be an increased focus on public input regarding the safety concerns of marketed drugs.[18]

Considering the aforementioned, is Big Data-driven AI the solution to the noted drug development problems? Big Data became a significant consideration for drug development around 2010, as computing technologies evolved rapidly and continued to grow their processing power.[5] This is supported by growing interest in high-capacity computational subfields of AI, as evidenced by an increase in the availability of literature between 2016 and 2020.[19] Furthermore, it should be noted that many companies are leaning towards the application of AI technologies, driven by Big Data-related needs.[20] Data utilization in drug development and regulatory outcomes primarily focuses on 4 key areas: informing drug development strategy, characterizing distinctions in approach among review divisions or therapeutic areas, detailed analysis of regulatory policy impact on drug development, and enhanced forecasting.[21] The data available in pharmaceutical literature can be found in formats such as text, plots and images, mathematical equations and

chemical structures.[22] The use of AI in conjunction with Big Data is believed to provide actionable insights that would provide solutions to the aforementioned problems in drug development. As such, the authors aimed to ascertain the role of AI in streamlining drug development and regulatory processes by providing collated information on the applications of AI and an overview of the AI-associated transformations in the regulatory industry based on current needs. Following this, the review identified and described the barriers limiting the integration of AI technologies and finally providing recommendations on the implementation of AI systems in drug development and regulatory processes.

Methods

Study Design

This study was conducted as a narrative review. The data sources utilized for this narrative review included 4 databases, namely, Cochrane Library, Medline (OVID), PubMed, and Scopus. The search strategy included a combination of the medical subject headings (MeSH) terms such as "artificial intelligence", "drug development", and "drug regulation". Boolean operators "AND" and "OR" were used in the search. The resultant articles were exported to EndNote (version 20) referencing manager tool. All duplicate articles were removed using EndNote.

The inclusion criteria included articles published in English from 2015 to present. This time frame was chosen considering the increasing amount of literature focusing on machine learning during this period, coinciding with the onset of the Big Data era beginning around 2010.[5,23] Furthermore, between 2015 and 2020, the utilization of AI in biotechnology and pharmaceuticals was noted as a significant contributor to the evolution of new drug formulations.[24] The selected period allowed for the assimilation of the most relevant and cutting-edge information on the applications of AI. The exclusion criteria included articles that were published in languages other than English, and articles that focused primarily on the applications of AI in clinical practice for diagnostics and patient care, but with no direct correlation to drug development applications such as in clinical trial settings. Furthermore, specific consideration was given to articles that provided examples of existing AI utilized in any stage of the drug development pipeline, from the preclinical stage to regulatory affairs.

Results and Discussion

A review of the literature revealed numerous subfields of AI along with drug development. These span the entire product lifecycle, including drug discovery, pharmaceutical product development, clinical trial design and monitoring, product manufacturing and management, and quality assurance controls.[25] The AI subfields noted in this literature search include Natural Language Processing (NLP), Machine Learning (ML), Deep Learning (DL), and Robotic Process Automation (RPA).

Definitively, the literature describes NLP as computational linguistics, which is a branch of applied AI and computational techniques that learn, understand, and produce human language content.[26] Machine learning (ML), on the other hand, refers to AI that does not rely on static algorithms to execute functions but rather learns from available data sets, thus effectively creating a machine that is capable of learning from experience and improving its functions.[27] This subfield of AI has generated considerable interest due to its potential in a wide variety of settings, like drug regulation.[28] This AI subdivides into ML-based techniques that include Support Vector Machines, Decision trees, K-nearest neighbors, Naïve Bayesian methods and DL.[29,30]

Considering that DL is an extension of ML, in this review, DL separates itself from traditional ML technology by using computational models that are made up of multiple processing layers that mimic the human neural network known as artificial neural networks (ANN). These networks learn representations of unstructured data with multiple layers of abstraction. DL methods outperform other ML-based approaches and include tools such as ANN-subfields like Convolutional Neural Networks, Recurrent Neural Networks, and Generative Adversarial Networks, as well as Stacked autoencoders and Boltzmann machines.[20]

Lastly, RPA refers to pre-configured software that has the capacity to autonomously execute processes, transactions and tasks.[28] It can be merged with NLP and ML to generate uniform datasets that are relevant to the analysis performed.[28] According to the authors, this is advantageous to information management systems that are utilized in drug development and regulatory processes, considering varying needs to generate commercially viable data.

Artificial Intelligence in Research and Development and Preclinical Stages of Drug Development

Currently, the drug development pipeline determines the probability of technical and regulatory success of a drug by assessing historical estimates driven by the current status of the development program and the specific disease under investigation. This information is then combined with insights from key opinion leaders and statistical analyses performed by drug sponsors to provide projections of the likelihood of a successful drug launch.[31] Most interestingly, the use of real-world data (RWD) presents a growing opportunity for guiding drug development strategy in the stages preceding the preclinical development.[32] However, it is important to note that Big Data and RWD are not synonymous, as RWD refers to observational studies that are similar to Big Data but focus specifically on patient health status and delivery of care.[33] RWD are used to develop real-world insights (RWI) and real-world evidence (RWE) that can be used to develop key portions of Target Product Profiles (TPPs). These TPPs are effective regulatory lifecycle management tools that facilitate dialogue between sponsors and regulators, allowing more efficient review times.[34]

Definitively, RWE can be understood as scientific evidence derived from the rigorous analysis of RWD with appropriate study methodology, which assists in guiding the product development process to compare assets based on forecasted population size, anticipated market share, revenue, and perceived advantage of therapies.[32] To support the process of taking a drug from R&D to market, entities such as IQVIA, Kantar Health, and IBM utilize RWD/RWE to provide actionable RWI-driven services to ensure cost-effective and efficient ways to get therapies to market.[32] This is supported by evidence that the availability of better quality information and the use of that information in decision-making can improve the delivery of new drugs to the market.[35] Conventional drug discovery methods were considered imperceptive, and hence methods based on modeling and projections, such as model-informed drug development (MIDD), were deployed within the industry to assess and identify potential risks that threaten the safety, efficacy and financial success of launched assets.[36,37] Thus, it can be inferred that this highlights a trend toward anticipatory drug development models that encourage early interaction with regulatory agencies and scientists. This is critical for aspects of development such as dose optimization, supportive evidence for efficacy, clinical trial design, and informing policy (Figure 1).[38,39]

Regulatory agencies like the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) encourage the use of MIDD for asset development.[40] The combination of ML and modeling of RWE are among the tools capable of supporting MIDD.[39] *In silico* models are an example of a favored MIDD approach that is currently utilized in the industry for the preclinical stages and includes subtypes such as quantitative structure-activity relationship (QSAR), non-compartmental analysis (NCA), physiology-based pharmacokinetic (PBPK modelling), and pharmacokinetic/pharmacodynamic (PK/PD) models.[40]

This review notes that the applicability of AI during these stages is quite broad, ranging from applications in the assessment of market needs for specific therapies to drug target discovery and generating relevant research questions.[32,41] This is exemplified by the use of com-

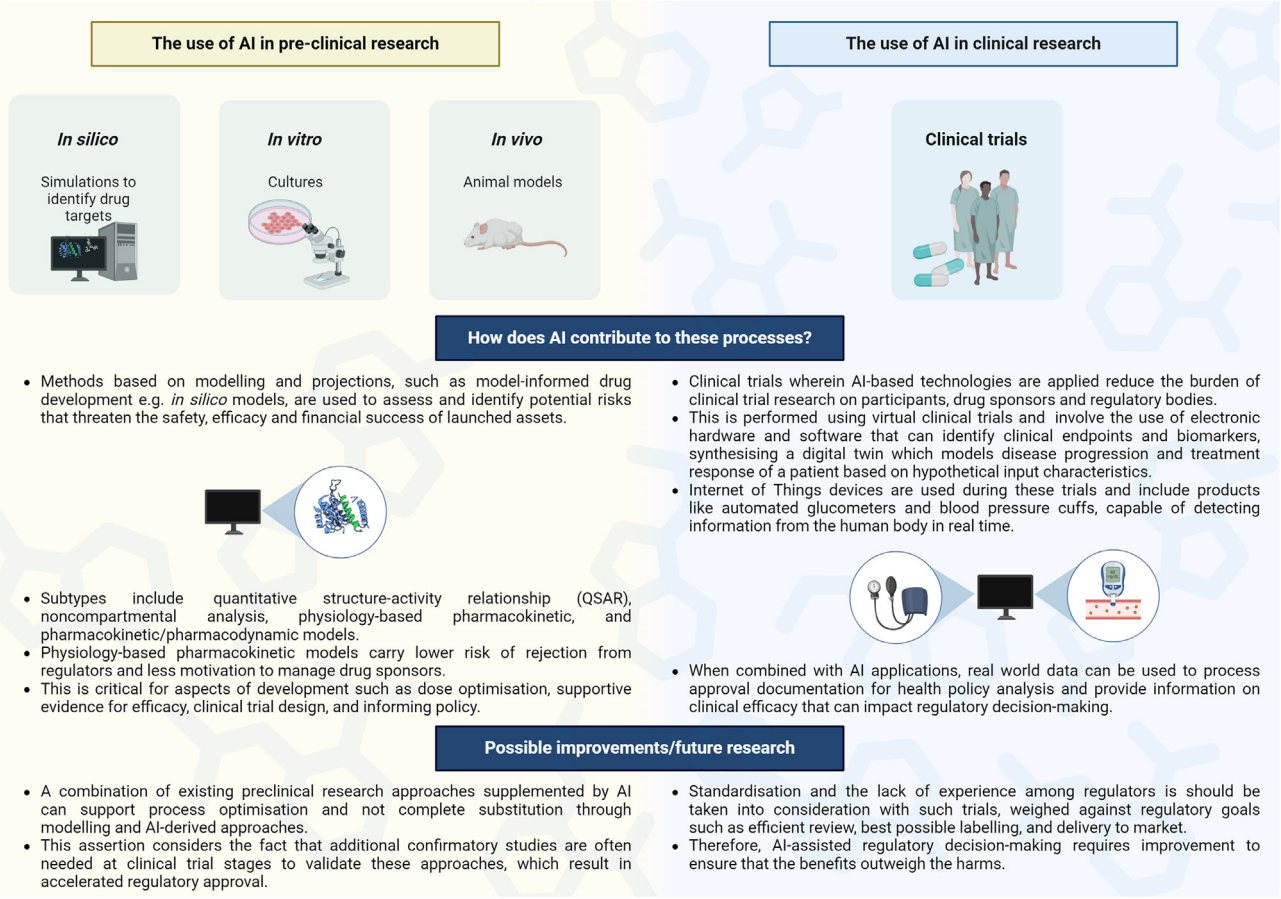

Figure 1. The use of AI in preclinical and clinical research. The image was created using BioRender (https://biorender.com/).

puter systems based on QSAR like DEREK, TOPKAT, COMPACT, MULTICASE, HazardExpert, and OncoLogic.[41] Commercially available software products like MATLAB, WinNonlin, and SAAM ll can perform linear and non-linear regression analysis utilizing an NCA approach. SimCYP, GatroPlus, and PK-SIM are examples of AI-supported PBPK models (Figure 1).[40]

It is worth noting that PBPK models represent a market-pull approach and not a technology-push approach, meaning that they generally carry a lower risk of rejection from regulators and requires less motivation to manage drug sponsors with respect to implementation.[37] This is advantageous as pharmacometrics models such as those mentioned are increasingly utilized by drug sponsors and supported by regulatory agencies to reduce human involvement during the experimental stages of drug development.[42] However, the preference for *in silico* models over *in vivo* (animal) models has led to an elevated risk of product development failures during the later stages.[26] Furthermore, studies have also cautioned that potential gains in the efficiency and reduction of expenses in preclinical research facilitated by AI can be minimized by failure in clinical trials or drugs with toxicity profiles not predicted by models.[32] As such, it can be argued that a combination of existing preclinical research approaches supplemented by AI can support process optimization and not complete substitution through modeling and AI-derived approaches. This assertion considers the fact that additional confirmatory studies are often needed at clinical trial stages to validate these approaches derived from RWE, which result in accelerated regulatory approval (Figure 1).[32]

Artificial Intelligence in the Clinical Stages of Drug Development

The trend for reducing the burden of experimentation on live subjects is an idea that further extends itself into clinical trials wherein AI-based technologies are applied to reduce the burden of clinical trial research on participants, drug sponsors and regulatory bodies.[42] This is exemplified by increasing emphasis toward establishing virtual clinical trials, also known as *in silico* or decentralized trials.[42,43] Virtual clinical trials involve the use of electronic hardware and software that can identify clinical endpoints and biomarkers, synthesizing a digital twin which models disease progression and treatment response of a patient based on hypothetical input characteristics. The digital twin model can then be used to predict how an individual patient will respond to the drug in certain conditions.[42,43] Furthermore, the virtual clinical trial technique has proven useful in recruiting patients for trials by analyzing data from heterogeneous sources (e.g., EHRs, social media, and other real-world databases), therefore supporting decentralized trials that do not focus on a single study site or minimize interactions with investigator sites for trial procedures. This would be enabled by Internet of Things (IoT) devices, which include products like automated glucometers and blood pressure cuffs, that are capable of detecting information from the human body in real time.[36,43,44] Virtually supported clinical trials have the advantage of enhancing patient centricity compared to traditional trials (Figure 1).[43]

There is also evidence for the use of ML techniques that predict transitions between clinical trial phases with high accuracy. There are common factors across therapeutic areas and phases that can be used to identify trials that are more likely to succeed or fail.[45] Furthermore, the utilization of NLP-based software and Random Forest (RF), a subtype of ML, has been useful in the advancement of clinical trials.[29,45] These AI achieve this by assessing unstructured and free text relating to eligibility criteria for clinical trials and determining the importance of variables in phase 2 and phase 3 clinical trials, respectively.[29,45] In addition, there is increased interest in the role of RWD in supporting expanded access to the use of drugs for patients suffering from debilitat-

ing and life-threatening conditions.[46] When combined with AI applications, such as NLP, these can be used to process approval documentation for health policy analysis and provide information on clinical efficacy that can impact regulatory decision-making.[46] However, it is necessary to take into consideration the need for standardization and the lack of experience among regulators with such trials, weighed against regulatory goals such as efficient review, best possible labeling, and delivery to market.[17,43] Therefore, it can be argued that AI-assisted regulatory decision-making requires improvement to ensure that the benefits outweigh the harms. Figure 1 illustrates the complementary nature of AI used in preclinical and clinical research for drug development. The use of AI in each stage is aimed at optimization of data generation and management of the data to maximize the likelihood of regulatory success.

Artificial Intelligence in the Registration and Regulation Stages of Drug Development

Applications of AI, such as random survival forecasting, an extension of RF, are well suited to support projections of new drug application (NDA) submissions, which informs the optimization of resource allocation and workload inside regulatory agencies.[38] Therefore ensuring timely and high-quality NDA reviews and approvals.[38] In addition, technologies such as the NLP-AI developed by Synchrogenix allow regulators to manage compliance information in more automated ways.[47] Ultimately, this wealth of data generated during the R&D/preclinical, and clinical stages of drug development is meant to facilitate registration for investigational new drugs (IND) and NDA, as well as support with obtaining market authorization of new drugs.[37] Liu et al. (2022) reported that the FDA's Center for Drug Evaluation and Research (CDER) noted an increase in AI/ML supported regulatory submissions. [48] In addition, there is an increasing trend among regulatory agencies with similar capabilities and philosophies to engage in collaborative work-sharing or reliance approaches, such as the Australia-Canada-Singapore-Switzerland-United Kingdom (ACCESS) Consortium.[49] Among these agencies, AI was utilized to optimize workflows of regulatory mechanisms aimed at improving assessments for market authorization of NDA and INDs.

Artificial Intelligence in Postmarket Safety Monitoring, Drug Repurposing, Manufacturing, and Pharmacovigilance

The application of AI can also be noted in post-market safety monitoring, drug repurposing, manufacturing, and pharmacovigilance, which all play a critical role in the drug development lifecycle. This review sought to weigh the implications associated with these activities as they have direct consequences on the delivery of therapies to market and are also dependent on the drug development value chain and its processes.

Drug Manufacturing and Formulation

Damiati[20] and Escotet-Espinoza et al[50] demonstrated in their findings that ANN are crucial tools for the pre-formulation aspects of drug development. During the pre-formulation stages, the physicochemical properties of a drug are assessed thus allowing for the determination of various physical parameters, such as its solubility, stability, interaction with excipients, and, ultimately, bioavailability.[20,50] Furthermore, a review conducted by Escotet-Espinoza et al[50] revealed various strategies for utilizing ANN to determine which coating components were needed in their formulation based on its effects on *in vitro* dissolution, film opacity and crack velocity.

Drug Repurposing

Application of AI in drug repurposing was exemplified by Manczinger et al[51], who described a ML algorithm (i.e., Support Vector Machine Learning algorithm) that demonstrated the ability to select for drugs that were already in clinical assessment studies for psoriasis and were further validated by *in vitro* and *in vivo* studies.[51] Methods such as these for drug repurposing are expected to become more efficient as mining of EHRs to retrospectively assess the effect of drugs gains feasibility.[52] This holds great value as the repositioning approach bypasses many of the pre-approval tests essential for newly developed therapeutic compounds.[53] Moreover, ML algorithms use collaborative filtering techniques to predict unknown drug-disease associations.[54] Various types of Big Data (e.g., genomic, phenotypic, clinical data, chemical structure) are publicly available for computational drug repositioning research, which shows promise in accelerating drug discoveries in areas such as cancer, as well as infectious and orphan diseases.[54] Integrative repositioning strategies for heterogeneous data proved useful in identifying novel applications for existing drugs.[51,54]

Pharmacovigilance and Postmarket Safety Monitoring

Pharmacovigilance supported by AI can be seen through applications such as the Web Crawler utilized by the Singapore Health Sciences Authority to monitor active alerts regarding product defects and potential adverse drug reactions (ADRs), which assist the agency in minimizing potential defective products from affecting the local market.[55] Additional examples of AI tools used in R&D and preclinical, clinical stages, registration, regulation, repurposing, manufacturing, and pharmacovigilance can be found in Supplementary Tables I, II, III and IV. These examples of AI in drug development serve as a proof of concept for the integration of AI in drug development operations. It should be noted that the authors of this paper are not affiliated with any of entities or software products and services mentioned in the paper.

Implications of Artificial Intelligence Application on Challenges in Drug Development

The scope of AI applications noted in this review is broad and ranges from preclinical use for target discovery to manufacturing, market authorization, and repurposing of existing products. Based on the results presented, it can be put forth that each of the AI contributes to mitigating the challenges associated with drug development as a whole. For example, AI systems like WEB-RADR and Vulcan address the cautious regulator issue by supporting regulatory functions and reducing the burden of their related activities on drug regulators. Furthermore, the technologies described in the various stages directly impact the operational aspects of the drug development process. The impact of the applications in terms of turnaround time and resource saving through the utilization of such AI presents an avenue for future research.

Although it is difficult to ascertain at this stage, it is likely that greater regulatory success will be seen in agencies that optimize workflows in favor of information sharing with regulatory agencies, key opinion leaders and different internal stakeholders within the drug development pipeline to help select for development assets that present the greatest value.[38,39] As it stands, AI will likely evolve considerably over the course of the next decade as it attracts greater investment and is deployed for more operations across the drug development sector. Within the scope of future research, additional questions will be raised about the current competitive framework of the pharmaceutical industry, as it pertains to the "first-to-market" approach used by many major drug development agencies, as seen with the "throw money at it tendency." This will require the agencies to take into the consideration various factors limiting the applicability of AI in drug development, the ever-evolving research landscape, and how to best optimize their regulatory intelligence strategies in favor of more cost-effective approaches for the delivery of efficacious drugs.[3]

Barriers Limiting the Use of Artificial Intelligence in Drug Development

Numerous factors, summarized in Figure 2, coincide with the applicability of AI in drug development that limit the utility of the technology. These range from issues relating to modeling and regulatory

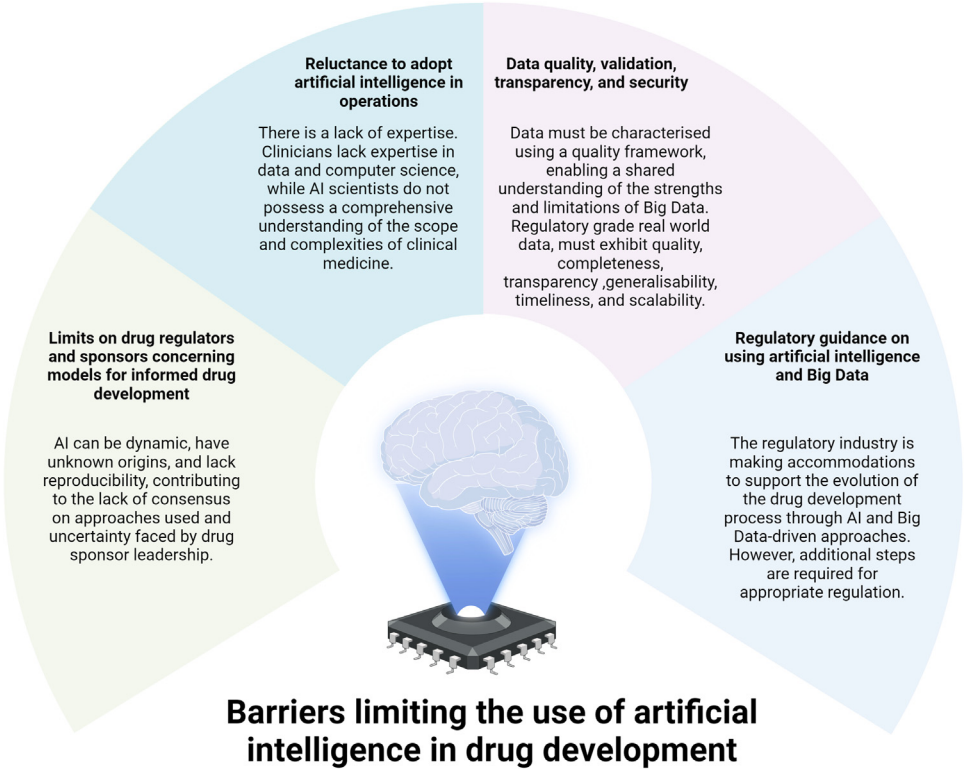

Figure 2. Barriers limiting the use of AI in drug development. The image was created using BioRender (https://biorender.com/).

Table 1
Sponsor and regulator challenges in MIDD

Regulator challenges	Sponsor challenges
Questions assessed by models are hardly described	Lack of guidance for cases of interest
Model objectives are not always clear and in line with the actual use of the model	Requirements for models are unclear
The adequacy of data is not described	Inconsistencies in opinions or issues of modelling relating to similar scientific questions
Models are not sufficiently evaluated or validated	Insufficient experience of regulators with MIDD
Poor reporting with aspects of models missing	Poor reporting on assessments

The data described in this table illustrates key challenges associated with MIDD an approach that is supported through AI and Big Data [53]
Abbreviation: MIDD – Model Informed Drug Development

frameworks for AI, data challenges, and interoperability between data sciences and clinical medicine, among others noted in the review. The sections that follow provide a cursory review of these barriers.

Limits on Drug Regulators and Sponsors Concerning Models for Informed Drug Development

Trustworthy AI needs to be built on principles of credibility, transparency, auditability, reliability and recoverability.[26] Considering these principles, Skottheim Rusten and Musuamba[56] describe the challenges noted in the literature associated with MIDD as they relate to regulators and sponsors (Table 1). Key to the regulator-associated challenges is the "black box" nature of many AI. This would mean that the logic and processing units which process data inputs to generate outputs from the AI would remain obscured.[57] Furthermore, AI can be dynamic, have unknown origins, and lack reproducibility, among other problems.[27,56] Central to the issues faced by the sponsors is the lack of consensus on approaches used and uncertainty faced by drug sponsor leadership on how far MIDD has actually improved drug development operations.[37,56] From this, it can be surmised that efforts for producing credible research on the value-add of AI in drug development operations in terms of financial and turnaround time gained is lacking (Figure 2).

These findings are key, as MIDD is expected to become a mainstay approach in drug development and regulatory decision-making moving forward.[58] As such, it can be expected that future evaluations of technologies affecting drug development will need to include their impact on MIDD, as well as necessitate the establishment of *good x practice* (*GxP*) with AI for example, Good Machine Learning Practice (GMLP).[19]

Reluctance to Adopt Artificial Intelligence in Operations

Clinicians and various role players in drug development processes often lack expertise in data and computer science, while AI scientists do not possess a comprehensive understanding of the scope and complexities of clinical medicine.[59] Consequently, this mismatch creates a disconnect between data science-driven AI technology, and the application of clinical knowledge. This cultural divide and cynicism stemming from past failures inform the disinterest noted among clinicians regarding AI.[59] In addition, many developers of AI-driven technologies are not adequately integrated into national health systems or drug sponsors, potentially limiting their awareness of the most pressing areas of need.[60] Therefore, there is an urgent demand for integrated platforms that foster coordination between these professionals and skillsets for the safe and meaningful use of AI in drug development. Similar sentiments have been expressed by the EMA, which called for collaborative evidence generation and improvement of scientific evaluations by 2025 (Figure 2).[61]

Data Quality, Validation, Transparency, and Security

Presently, there is a need to characterize data using a quality framework which enables a shared understanding of the strengths and limitations of Big Data.[27] Regulatory grade RWD, which is anticipated to support AI-driven drug development, must exhibit quality, completeness,

transparency, generalizability, timeliness, and scalability (Figure 2).[32] However, much of RWD currently exists in unstructured formats from which relevant data must be interpreted and stored in new structured formats[28] thus, requiring considerable time investment. Presently, regulatory submissions comprise information in Adobe portable document format (PDF). However, this is not the most optimal format to exploit AI and ML tools.[49]

Initiatives are underway to develop structured content management systems whereby a database holds human and machine-readable blocks of information and allows the importation of such data into a linked document.[49] Based on the evidence generated in this review, it can be assumed that the likelihood of success for such an initiative would be bolstered by the successful implementation of the electronic common technical document (eCTD), given the standardization approaches used in eCTDs. Furthermore, it would be advisable for organizations, drug sponsors and regulators alike, to consider using organizational readiness assessments for AI within their strategic planning. These assessments may be standardized based on lessons generated by previous frameworks and adjusted based on context specific needs. Such assessments take into account critical features of data management for the deployment of AI, like technology infrastructure, data quality, and analytics, as well as cyber security.[59] The authors of this review recommend that regulators lead the development of organizational readiness assessments thus allowing drug sponsors to measure their processes against a standardized national or international framework. Approaches such as this have been exemplified through the FDA Framework for Real World Evidence which also accounts for data standards for integration and submission.[28] Thus, ensuring minimised risks such as the "black box" problem associated with AI.

In contrast with the "black box" problem of many AI algorithms, transparent AI, set to appropriate standards, would inform the user of the parameters utilized to generate their predictions.[44] Considering this, the authors of this review encourage regulators to reject the "black box" issues. The code that creates AI algorithms requires the same post-marketing surveillance mechanisms that drugs have.[27] This feeds into validation and regulation principles for AI in drug development, which ask pertinent questions such as, "*What metrics is the algorithm trained on?*". The performance of an algorithm is dependent on the datasets on which it is trained. Thus, the output will reflect the distribution, variability, and complexity of the data in the training dataset and potentially the biases of those training the algorithm such as selective bias.[23,27] Opposing considerations for the protection of AI algorithms as intellectual property, against concerns of health data privacy come into play. However, it is important to maintain health privacy at the center of the considerations made when taking into account questions on the extent to which consent can be provided by an individual on how their data is used in predictive modeling. [4] This requires drug sponsors and regulators to maintain balance between transparency and privacy in the use of AI, taking into account the origins, ownership, formatting, flow and accessibility of the data. [4,57] Reproducibility of data is another challenge that arises due to the dynamic nature of ML-generated datasets, which may sometimes have unknown origins and incomplete metadata descriptions, thus limiting analysis applications as well as regulatory fidelity.[27,29] ML algorithms also create the unique conundrum of unpredictable future behaviors of the machine, thus presenting issues on the liability of the user for outcomes associated with the AI.[23]

The Japanese Pharmaceuticals and Medical Devices Agency outlines AI/ML-associated risks as dependent on the performance of the technology. Therefore, higher-performing AI carry more significant risks in the incidence of cyberattack and failed reliability, which is a major concern for AI applied on large-scale data like those utilized in pharmacovigilance and multi-centre clinical trials.[19,57] This necessitates secure data warehouses, which are a repository of large volumes of data collected from multiple warehouses, as well as the need for robust security systems that ensure authorized use, identification of author records, and audit trails to trace any data changes.[36,43]

Data warehouses, such as these, would require management through available technologies such as highly distributed storage systems, blockchain, and cloud computing, which offer components that assist in the ML life cycle.[62] These technologies allow for easy and scalable access to computational resources and an ecosystem of tools developed to aid data scientists in working effectively with ML modelling.[62,63] For example, this would mean that a clinical trial patient may authorize a medical doctor to access sensitive data. However, only a fraction of that data may be available for a medical researcher in drug development.[57]

These considerations effectively describe Machine Learning and Operations (MLOps), which is a collaborative effort by data engineers and scientists, as well as operations professionals, to cover the entire life cycle of ML modeling in production environments such as drug development.[63] The emergence of MLOps as it pertains to drug development connects the disjointed efforts between pharmaceutical professionals, AI modelers, and service providers for hosting production-grade ML models and to enable collaborations in a systematic way of working and cloud-based software to support.[63] It is worth noting that data uploaded in real-time into a cloud-based data-sharing environment potentially blurs the distinction between pre- and postapproval data flow, which may carry regulatory implications that have not yet been defined.[49] Therefore, regulatory agencies will likely be faced with the task of reviewing existing workflows for dossier submission and the adaptability of these processes in the face of AI-based transformations.

Regulatory Guidance on Using Artificial Intelligence and Big Data

Literature provides some evidence of the regulatory industry making accommodations to support the evolution of the drug development process through AI and Big Data-driven approaches. However, it is important to note that developing technologies will not fit neatly into current regulatory frameworks, and additional steps are required for appropriate regulation (Figure 2). Many data laws as they currently exist are inadequate when it comes to protecting the rights of patients, as exemplified by laws like the Genetic Information Non-discrimination Act (2008) and Health Insurance Portability and Accountability Act (1996) in the US, which currently does not adequately cover the vast majority of health data and can only remove identifiers.[4] Furthermore, such laws currently do not cover many entities like Google, IBM and Apple that engage with health data through IoT devices and ML.[4,44] In 2017, the CDER undertook a multi-year initiative aimed at modernizing science and the regulation of new drugs. This process revealed that the industry could benefit from the standardization of processes, increased transparency, integration of drug review documents, and strengthening workflows through tools and technologies that improve new drug applications.[60] Alemayehu et al. (2022) asserts that that sponsors should familiarize themselves with guidance documents on digital systems and appropriate record maintenance requirements considering the lack of knowledge and regulatory experience with tools like virtual clinical trials driven by AI.[43] This is necessitated by the need for quality data and good data practices. Existing guidelines addressing data integrity, patient safety and confidentiality include the FDA guidance on using electronic source data, the EMA reflection paper on expectations for source data, and the European Union Data Protection regulation, among others.[4,43] However, a less-than-ideal picture is painted when assessing the regulatory landscape in regions such as Africa, where, according to the World Health Organization, only 4 regulatory authorities, at the time, operated at a level of maturity that can be defined as stable, well-functioning and integrated, according to the Global Benchmarking Tool. As such, countries within this region, as well as others in the global South, will require substantial support in establishing uniformity in drug regulation and development processes, while tackling the advent of AI.[64] This process, within the growing and emerging markets like those in Africa, can begin with recognition of common objectives in existing guidelines and reports shared by regulatory authorities in other regions of the world, such as the EU's Ethics Guidelines for Trustworthy AI (2019.)[23,65] From this, appropriately contextualised frameworks may be

developed by agencies on the continent, accounting for data quality, the breadth of regulatory decision-making and its associated consequences, along with synergies available with other agencies.[27] Furthermore, the establishment of regional public health agencies such as the Africa Centre for Diseases Control and Prevention (2016) positions the continent favorably by having a central convenor of the shared public health vision of the states represented.[66] As highlighted by the authors, demonstrated through initiatives like the African Union (AU) Model Law on Medical Products Regulation (2014), and the AU Treaty for the Establishment of the African Medicines Agency (2019) there is an aspiration for regulatory agencies across the continent to sufficiently manage requirements for drug regulation in an ecosystem that relies on work-sharing, transparency, and efficiency.[64,67]

In order to achieve this, regulatory agencies and sponsors in emerging markets needs to follow examples set out by collaborative efforts like the International Medical Device Forum, which has developed some of the earliest known guidelines and international standards for AI in clinical trials.[68] These guidelines, known as the Consolidated Standards for Reporting Trials (CONSORT) and Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT), provide guidance for randomized trials and protocols, and adaptations (CONSORT-AI and SPIRIT-AI), have since been made to incorporate AI considerations within them.[65,68] Furthermore, the International Council for Harmonization (ICH) of Technical Requirements of Pharmaceuticals for Human Use, has released the M15: Model-Informed Drug Development General Principles Guideline which seeks to broadly cover good practices and principle in MIDD for regulatory submissions.[69] These are essential considering the central role that MIDD currently plays in AI implementation across preclinical and clinical drug development stages.

Limitations

The key limitations associated with this study are tied closely to the nature of the narrative review methodology. The thematic analysis performed in this paper followed appropriate conventions of the review type, assessing the literature based evidence collated from search results drawn from key terms. This means that the findings of the paper are limited primarily to the scope of the search terms and are unable to give insight on literature that may be available beyond what was sought out in the initial identification of the literature database. Ultimately, in relation to an ever-changing technology with respect to AI, additional findings may exist beyond the scope of what has been addressed herein. Furthermore, this review does not offer quantifiable evidence on the improvements generated by the use of AI in drug development and relies on previously reported data from other studies. However, this highlights an interesting research gap that can be addressed by parametric measures in future studies. These measures could assess evidence of enhancement or deterioration in drug development processes and regulatory outcomes. Factors such as time spent in the development pipeline, operational considerations, and financial benefits could be further explored to provide a comprehensive overview of the subject.

Conclusion and Recommendations

Based on the findings of this paper, it can be categorically stated that AI is a strategic lever for drug development, and its utility as a statistical learning method designed for large and dynamic datasets has been extensively reported in the literature. The findings of this review indicate that AI functions as a context-specific tool to support operations at different stages of drug development. AI primarily contributes to enhancing efficiency in these operations by providing actionable knowledge through which these functions can be executed. As exemplified by the use of AI technologies such as NLP and DL, AI in drug development has gradually moved past the peak of high expectations and is now entering the stage where interest wanes from failed experiments, and investment continues to grow in areas where products have demonstrated satisfactory results.

Key strategies for implementing AI in the pharmaceutical industry have been noted and include fostering awareness, encouraging education and building expertise in AI, establishing dedicated AI entities, roadmaps for developing and integrating AI applications, implementing systems for data access storage and sharing, and developing diverse AI portfolios that are responsive according to organizational readiness.[59] These are key recommendations for agencies within Africa that are currently underprepared as per the observations of the authors, based on the lack of evidence from the region that was generated by this review. Furthermore, drug sponsors and regulatory authorities have the responsibility of investing in their workforce skills by training regulatory scientists in digital literacy alongside scientific methods. This is because the ability to access and analyse data to enrich product knowledge and inform regulatory decision-making is key expertise, along with automation of tasks supported by digital tools.[49] Furthermore, investigations that produce statistically relevant data into the financial and operational gains made through AI are required to support the optimization of its utility in the industry.

Author Contribution

Linda Nene drafted the article, conducted the literature research, collected the data, analyzed, and interpreted the results and wrote the manuscript. Brian Thabile Flepisi, Sarel Jacobus Brand, Charlise Basson, and Marissa Balmith were responsible for conceptual contributions as well as reviewing and editing the manuscript.

Consent for Publication

All authors listed on the title page have read the manuscript, attest to the validity and legitimacy of the data and its interpretation and agree to its submission in Clinical Therapeutics.

Availability of Data and Materials

No additional data has been generated.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

1. Berdigaliyev N, Aljofan M. An overview of drug discovery and development. *Future Med Chem.* 2020;12:939–947.
2. Sidders B, Johnson J, Khosla S. Unlocking the potential of data and AI-driven drug discovery & development [Internet]. *Astrazeneca.* 2023. [Accessed August 30, 2023]. Available from. https://www.astrazeneca.com/what-science-can-do/topics/data-science-ai/unlocking-potential-data-ai-driven-drug-discovery-development.html.

3. Mayer M, Canedo A, Dinh T, et al. Potential use of artificial intelligence for regulatory intelligence: biopharmaceutical industry's views. *Ther Innov Regul Sci*. 2019;53:759–766.
4. Price WN, Cohen IG. Privacy in the age of medical big data. *Nat Med*. 2019;25:37–43.
5. Zhu H. Big data and artificial intelligence modeling for drug discovery. *Annu Rev Pharmacol Toxicol*. 2020;60:573–589.
6. Chen J, Luo X, Qiu H, et al. Drug discovery and drug marketing with the critical roles of modern administration. *Am J Transl Res*. 2018;10:4302–4312.
7. Scannell JW, Blanckley A, Boldon H, Warrington B. Diagnosing the decline in pharmaceutical R&D efficiency. *Nat Rev Drug Discov*. 2012;11:191–200.
8. Van Norman GA. Overcoming the declining trends in innovation and investment in cardiovascular therapeutics: beyond EROOM's Law. *JACC: Basic Transl Sci*. 2017;2:613–625.
9. Barker RW, Scannell JW. The life sciences translational challenge: the European perspective. *Ther Innov Regul Sci*. 2015;49:415–424.
10. Forum on Neuroscience and Nervous System Disorders, Board on Health Sciences Policy, Institute of Medicine. *Improving and Accelerating Therapeutic Development for Nervous System Disorders: Workshop Summary [Internet]*. Drug Development Challenges. National Academies Press (US); 2014 [Accessed September 1, 2023]. Available from *https://www.ncbi.nlm.nih.gov/books/NBK195047/* .
11. Tormay P. Big data in pharmaceutical R&D: creating a sustainable R&D engine. *Pharm Med*. 2015;29:87–92.
12. Scannell JW, Bosley J. When quality beats quantity: decision theory, drug discovery, and the reproducibility crisis. *PLoS One*. 2016;11:e0147215.
13. Bowen A, Casadevall A. Increasing disparities between resource inputs and outcomes, as measured by certain health deliverables, in biomedical research. *Proc Natl Acad Sci U S A*. 2015;112:11335–11340.
14. Dowden H, Munro J. Trends in clinical success rates and therapeutic focus. *Nature Rev Drug Discov*. 2019;18:495–496.
15. Al-Worafi YM. Medications registration and marketing: safety-related issues. *Drug Safety in Developing Countries [Internet]* Elsevier; 2020:21–28.
16. Forum on Drug Discovery D, Policy B on HS, Division H and M, National Academies of Sciences E. Challenges and opportunities in regulatory science [Internet]. Advancing the discipline of regulatory science for medical product development: an update on progress and a forward-looking agenda: Workshop Summary. National Academies Press (US); 2016 [Accessed October 5, 2022]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK379029/.
17. Lassof P, Poirieux O. The evolution of regulatory affairs [Internet]. IQVIA. 2018 [Accessed February 3, 2022]. Available from: https://www.iqvia.com/library/white-papers/the-evolution-of-regulatory-affairs
18. Balfour H. Cutting the financial and time costs of regulatory affairs with automation. European pharmaceutical review [Internet]. 2020 [Accessed September 1, 2023]; Available from: https://www.europeanpharmaceuticalreview.com/article/116872/cutting-the-financial-and-time-costs-of-regulatory-affairs-with-automation/
19. Dri DA, Massella M, Gramaglia D, et al. Clinical trials and machine learning: regulatory approach review. *RRCT*. 2021;16:341–350.
20. Damiati SA. Digital pharmaceutical sciences. *AAPS PharmSciTech*. 2020;21:206.
21. Robertson AS, Reisin Miller A, Dolz F. Supporting a data-driven approach to regulatory intelligence. *Nat Rev Drug Discov*. 2021;20:161–162.
22. Viswanath S, Fennell JW, Balar K, Krishna P. An industrial approach to using artificial intelligence and natural language processing for accelerated document preparation in drug development. *J Pharm Innov*. 2021;16:302–316.
23. Basu T, Engel-Wolf S, Menzer O. The ethics of machine learning in medical sciences: where do we stand today? *Indian J Dermatol*. 2020;65:358.
24. Sethuraman N. Artificial intelligence: a new paradigm for pharmaceutical applications in formulations development. *IJPER*. 2020;54:843–846.
25. Paul D, Sanap G, Shenoy S, et al. Artificial intelligence in drug discovery and development. *Drug Discovery Today*. 2021;26:80–93.
26. Kalaiselvan V, Sharma A, Gupta SK. Feasibility test and application of AI in healthcare"—with special emphasis in clinical, pharmacovigilance, and regulatory practices. *Health Technol*. 2021;11:1–15.
27. Cave A, Brun NC, Sweeney F, et al. Big data – how to realize the promise. *Clin Pharmacol Ther*. 2020;107:753–761.
28. Zou KH, Li JZ, Imperato J, et al. Harnessing real-world data for regulatory use and applying innovative applications. *JMDH*. 2020;13:671–679.
29. Gao D, Chen Q, Zeng Y, et al. Applications of machine learning in drug target discovery. *CDM*. 2020;21:790–803.
30. Rashid MBMA. Artificial intelligence effecting a paradigm shift in drug development. *SLAS Technol*. 2021;26:3–15.
31. Vergetis V, Skaltsas D, Gorgoulis VG, Tsirigos A. Assessing drug development risk using big data and machine learning. *Cancer Res*. 2021;81:816–819.
32. Dagenais S, Russo L, Madsen A, et al. Use of real-world evidence to drive drug development strategy and inform clinical trial design. *Clin Pharma Therap*. 2022;111:77–89.
33. Okada M. Big data and real-world data-based medicine in the management of hypertension. *Hypertens Res*. 2021;44:147–153.
34. Breder CD, Du W, Tyndall A. What's the regulatory value of a target product profile? *Trends Biotechnol*. 2017;35:576–579.
35. Ringel MS, Scannell JW, Baedeker M, Schulze U. Breaking Eroom's law. *Nat Rev Drug Discov*. 2020;19:833–834.
36. Gupta PK, Nawaz MH, Mishra SS, et al. *Sustainable and Energy Efficient Computing Paradigms for Society [Internet]*. New age approaches to predictive healthcare using in silico drug design and internet of things (IoT) editors. Cham: Springer International Publishing; 2021 [cited 2022 Oct 6]. p. 127–51. (EAI/Springer Innovations in Communication and Computing). Available from. https://link.springer.com/10.1007/978-3-030-51070-1_8.
37. Lesko LJ. Perspective on model-informed drug development. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:1127–1129.
38. Hu M, Babiskin A, Wittayanukorn S, et al. Predictive analysis of first abbreviated new drug application submission for new chemical entities based on machine learning methodology. *Clin Pharmacol Ther*. 2019;106:174–181.
39. Wang Y, Zhu H, Madabushi R, et al. Model-informed drug development: current us regulatory practice and future considerations. *Clin Pharmacol Ther*. 2019;105:899–911.
40. Maharao N, Antontsev V, Wright M, Varshney J. Entering the era of computationally driven drug development. *Drug Metabol Rev*. 2020;52:283–298.
41. Liu K, Ding R, Xu H, et al. Broad-spectrum profiling of drug safety via learning complex network. *Clin Pharmacol Ther*. 2020;107:1373–1382.
42. Viceconti M, Pappalardo F, Rodriguez B, et al. In silico trials: verification, validation and uncertainty quantification of predictive models used in the regulatory evaluation of biomedical products. *Methods*. 2021;185:120–127.
43. Alemayehu D, Hemmings R, Natarajan K, Roychoudhury S. Perspectives on virtual (remote) clinical trials as the "new normal" to accelerate drug development. *Clin Pharma and Therapeutics*. 2022;111:373–381.
44. Bonifazi F, Volpe E, Digregorio G, et al. Machine learning systems applied to health data and system. *Eur J Health Law*. 2020;27:242–258.
45. Feijoo F, Palopoli M, Bernstein J, et al. Key indicators of phase transition for clinical trials through machine learning. *Drug Discovery Today*. 2020;25:414–421.
46. Polak TB, Rosmalen JUyl – de Groot CA. Expanded access as a source of real-world data: an overview of FDA and EMA approvals. *Br J Clin Pharmacol*. 2020;86:1819–1826.
47. Taranum S. Trends in regulatory writing: a brief overview for aspiring medical writers. *MEW*. 2019;28:62–69.
48. Liu Q, Huang R, Hsieh J, et al. Landscape analysis of the application of artificial intelligence and machine learning in regulatory submissions for drug development from 2016 to 2021. *Clin Pharma Therap*. 2023;113:771–774.
49. Macdonald JC, Isom DC, Evans DD, Page KJ. Digital innovation in medicinal product regulatory submission, review, and approvals to create a dynamic regulatory ecosystem—are we ready for a revolution? *Front Med [Internet]*. 2021;8:1–12. [Accessed October 6, 2022]Available from. https://www.frontiersin.org/articles/10.3389/fmed.2021.660808 .
50. Escotet-Espinoza MS, Rogers A, Ierapetritou MG. Optimization methodologies for the production of pharmaceutical products. In: Ierapetritou MG, Ramachandran R, eds. *Process Simulation and Data Modeling in Solid Oral Drug Development and Manufacture [Internet]*. New York, NY: Springer New York; 2016:281–309.
51. Manczinger M, Bodnár V, Papp B, et al. Drug repurposing by simulating flow through protein-protein interaction networks. *Clin Pharmacol Ther*. 2018;103:511–520.
52. Himmelstein DS, Lizee A, Hessler C, et al. Systematic integration of biomedical knowledge prioritizes drugs for repurposing. *eLife*. 2017;6:e26726.
53. Lotfi Shahreza M, Ghadiri N, Mousavi SR, et al. A review of network-based approaches to drug repositioning. *Brief Bioinform*. 2018;19:878–892.
54. Li J, Zheng S, Chen B, et al. A survey of current trends in computational drug repositioning. *Brief Bioinform*. 2016;17:2–12.
55. Ang PS, Teo DCH, Dorajoo SR, et al. Augmenting product defect surveillance through web crawling and machine learning in Singapore. *Drug Saf*. 2021;44:939–948.
56. Skottheim Rusten I, Musuamba FT. Scientific and regulatory evaluation of empirical pharmacometric models: an application of the risk informed credibility assessment framework. *CPT Pharmacometrics Syst Pharmacol*. 2021;10:1281–1296.
57. Tozzi AE, Cinelli G. Informed consent and artificial intelligence applied to RCT and Covid-19. *BioLaw J - Rivista di BioDiritto*. 2021:97–108 Paginazione.
58. Madabushi R, Seo P, Zhao L, et al. Review: role of model-informed drug development approaches in the lifecycle of drug development and regulatory decision-making. *Pharm Res*. 2022;39:1669–1680.
59. Scott IA, Abdel-Hafez A, Barras M, Canaris S. What is needed to mainstream artificial intelligence in health care? *Aust Health Review*. 2021;45:591–596.
60. Morley J, Murphy L, Mishra A, et al. Governing data and artificial intelligence for health care: developing an international understanding. *JMIR Form Res*. 2022;6:e31623.
61. Hines PA, Guy RH, Humphreys AJ, Papaluca-Amati M. The European Medicines Agency's goals for regulatory science to 2025. *Nat Rev Drug Discov*. 2019;18:403–404.
62. Mamoshina P, Ojomoko L, Yanovich Y, et al. Converging blockchain and next-generation artificial intelligence technologies to decentralize and accelerate biomedical research and healthcare. *Oncotarget*. 2017;9:5665–5690.
63. Spjuth O, Frid J, Hellander A. The machine learning life cycle and the cloud: implications for drug discovery. *Exp Opin Drug Discov*. 2021;16:1071–1079.
64. Ncube BM, Dube A, Ward K. Establishment of the African Medicines Agency: progress, challenges and regulatory readiness. *J Pharmaceut Policy Pract*. 2021;14:29.
65. Crigger E, Reinbold K, Hanson C, et al. Trustworthy augmented intelligence in health care. *J Med Syst*. 2022;46:12.
66. Africa CDC. About Us [Internet]. Africa CDC. [Accessed May 25, 2024]. Available from: https://africacdc.org/about-us/.
67. Africa CDC. African Medicine Agency (AMA) Treaty | African Union [Internet]. 2020 [Accessed May 25, 2024]. Available from: https://au.int/en/pressreleases/20200205/african-medicine-agency-ama-treaty.
68. Ibrahim H, Liu X, Rivera SC, et al. Reporting guidelines for clinical trials of artificial intelligence interventions: the SPIRIT-AI and CONSORT-AI guidelines. *Trials*. 2021;22:11.
69. ICH. ICH Official web site : ICH [Internet]. 2022 [Accessed May 21, 2024]. Available from: https://database.ich.org/sites/default/files/ICH_M15_ConceptPaper_Final_2022_1102.pdf.